THE JOURNAL

OF THE

American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 167, NO. 6 CHICAGO, ILLINOIS JUNE 7, 1958
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SOME RECENT ADVANCES IN NUTRITION

Tom D. Spies, M.D., Birmingham, Ala.

A large part of human disease is chemical rather than bacterial in origin, and in diseases of chemical origin the trouble may be either excess or deficiency. Twelve case histories are here given to illustrate the fact that deficiency states resulting from poor diets are still important and sometimes puzzling. Mental symptoms disappeared when a man was finally treated with nicotinic acid for a long-standing dermatitis which was pellagra. A man of excessively frugal habits suffered from spells of increasing weakness; he was able to return to work after a series of hemorrhages led to the diagnosis of scurvy, which was remedied promptly by the oral administration of ascorbic acid. In many cases, however, the deficiency is more complex; the effect on the patient is a general biological blight, and a spectacular response follows the administration of complex foodstuffs such as nonfat dry milk solids. In some deficiencies anorexia and glossitis are prominent symptoms; breaking this vicious circle with folic acid in one case led to the appearance of a voracious appetite and the complete restoration of a patient who had been near death from severe macrocytic anemia. The body cells can recover to an amazing degree from these chemical upsets. The deficiency diseases bring crushing burdens and stark tragedies; their prevention is a significant part of actual medical practice.

TODAY GERMS ARE not our principal enemy. Our chief medical adversary is what I consider a disturbance of the inner balance of the constituents of our tissues, which are built from and maintained by necessary chemicals in the air we breathe, the water we drink, and the food we eat. Persons who are afflicted with "rheumatism" or "cancer," for example, are not the victims of germs but of altered chemistry. For a generation we have worked on the concept that our cells are never static and that in time they must be replaced in varying degrees by the nutrients obtained from food. More specifically, our working hypothesis has been that all disease is chemical and, when we know enough, chemically correctable.

Malnutrition or undernutrition may be either the cause or the result of ignorance and poverty. (More than half the population of the world is on the verge of starvation from lack of food.) Coexisting nutritional disorders complicate all the problems of the sick, and there seems little likelihood of a final solution of the great problems of medicine until we can obtain optimum nutrition. Great progress has been made in recent years, and it is gratifying to us to see that our recommended methods of coping with nutritional problems are being used so widely. If our efforts in years to come are to bring equally important information, we must think in broader terms and we must do so promptly. I can hear many saying, "Today Americans live better than ever before." It is gratifying to have had a part in creating this exciting era. Certainly the science of human nutrition is now on an immeasurably higher plane than we found it a

From the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago.
Read in part before the General Scientific Meeting at the 106th Annual Meeting of the American Medical Association, New York, June 3, 1957.

few years ago. Yet we must continue the search for a still better understanding of the role of nutrition in maintaining a better balance in the tissues.

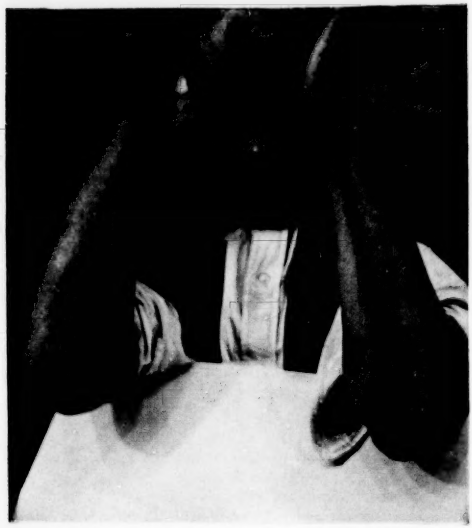

Fig. 1 (case 1).—Chronic pellagrous dermatitis in Negro man aged 50.

As physicians, let us face a number of our most difficult problems. We know that disease is as old as living matter; we know that the therapy we often apply to overcome it is little understood in day-to-day practice. In this day in which vitamins, for example, are so much more appreciated and accepted, vast groups of people have freedom from deficiency disorders. Still, an apparent paradox makes teaching of the diagnosis of deficiency states difficult, for today the so-called classic case is the rare case and the so-called atypical or mild case is the usual one. We will show a few illustrations of characteristic lesions which physicians did not recognize in their earliest stages as diagnostic, with the result that the patient had months or years of unnecessary ill health.

Deficiency States

Case 1.—In figure 1 we see chronic pellagrous dermatitis in a Negro man 50 years of age. For over 20 years he had not been well, and during the spring and fall he felt particularly weak and irritable. At times he was confused mentally. During this period of time he had easy fatigability and frequently he stayed in bed for several weeks. He was unable to work and on occasion he was unable to care for himself. His care and even his food had to be provided by others. Dramatic improvement followed the oral administration of 50 mg. of nicotinic acid 10 times daily. Within two months he obtained work, and we advised him as to what foods he should eat.

This patient did not develop a sore mouth or diarrhea at any period of his illness, and to some observers lack of these symptoms was confusing as far as the diagnosis of pellagra was concerned. Still further confusion arose because of the fact that the incidence of pellagra among the Negro population of Alabama was only 10% as high as among white people. True endemic pellagra in the southern part of the United States is virtually nonexistent at the present time, and younger physicians rarely think of it in making a differential diagnosis.

Case 2.—The boy shown in figure 2 was from a so-called good family. He was stunted in growth, did not do well in school, and had periodic soreness in the corners of his mouth. Frequently he had irritation of the eyes associated with photophobia. This type of cheilosis in the absence of any known allergy and in the presence of a diet which, according to our standards, was conspicuously low in riboflavin led us to consider riboflavin deficiency. He responded to the administration of 5 mg. of riboflavin orally three times daily. The cheilosis disappeared and has not returned during five years of observation. Throughout this period of time he has done better in school than he ever had before and has not had photophobia or any disturbance of his eyes.

Deficiencies of riboflavin and iron are frequent among underfed women who have given birth to several children and among children in the United States.

Case 3.—Figure 3, showing hemorrhage into the tissues, presents a diagnostic problem. This man had no teeth; therefore, we could find no gingival lesions of scurvy. The plasma

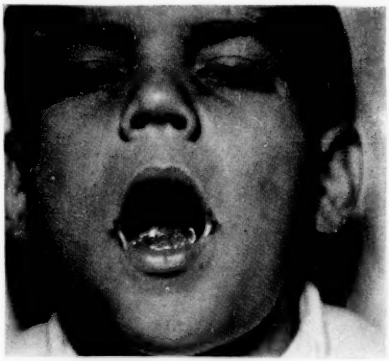

Fig. 2 (case 2).—Boy with riboflavin deficiency.

ascorbic acid level was zero. After a thorough physical examination and careful history, we made a diagnosis of scurvy. He was a bachelor who for a number of years had eaten by

himself. He drank some whiskey and rarely ate citrus fruit, vegetables, or lean meat. In fact, he did not remember the last time he had eaten any of these foods. For years he had what he called "ups and downs," periods of extreme weakness, and generally felt "no good." Prior to the appearance of the hemorrhagic areas shown in figure 3 he had had minor hemorrhages into his tissues from time to time. He responded promptly to 200 mg. of ascorbic acid administered orally three times a day. The hemorrhagic areas disappeared, his strength and feeling of well-being increased, and within three weeks he was able to return to work. We advised him as to what foods he should eat; he followed instructions and has not had a relapse since.

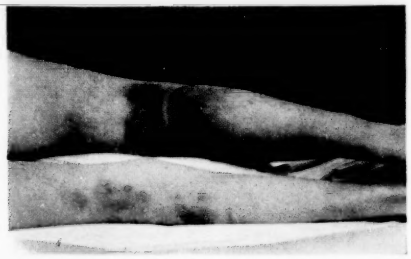

Fig. 3 (case 3).—Hemorrhage into tissues of man with scurvy.

The prompt disappearance of the vague symptoms of ill health in this patient after ascorbic acid therapy suggests the necessity of early treatment and of prompt and adequate treatment.

CASE 4.—Figures 4 and 5 show the nails and face of a woman who for many years had had excess menstrual bleeding and had eaten a poor diet. Her general pallor and the appearance of her fingernails suggested an underlying iron deficiency. After eight months of treatment with ferrous sulfate, her nails were almost normal and she was strong enough to work again. An interesting feature of this case is that she had had a poor diet and periods of menstrual hemorrhage for years. Because some of the previous observers noticed the severe anemia, weakness, but lack of low color index, they gave her intensive therapy with folic acid and vitamin B_{12}. Needless to say, a disturbance due to a lack of iron did not respond.

A deficiency of iron, of course, frequently is the cause of anemia in women and in children. It is important to maintain proper hemoglobin values throughout the latter part of infancy; however, many times iron is not taken in adequate amounts or frequently enough because it is not readily acceptable to the young. Also, the physician often fails to think about it.

Diagnostic Significance of Lesions Affecting Oral Tissues

The response of the alimentary tract to inadequate diets never has been studied as much as it deserves. The tissues lining the cavity of the mouth are easily examined and the examination causes no discomfort to the patient. In our 30 years of studying deficiency diseases, my associates and I have been impressed by the frequent appearance of lesions in the mucous membranes of the oral cavity, tongue, and gingivae. In a series of 914 consecutive patients admitted to the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala., the presenting symptom in 329 of these patients was soreness of the mouth and tongue.[1] From the point of view of their specific chemical etiology, the lesions affecting the oral tissues frequently are mixed and in many instances a number of therapeutic agents are required for complete treatment. Because of the similarity of some of the lesions due to a deficiency of nicotinic acid, vitamin B_{12}, or folic acid, specific diagnosis is difficult.

CASE 5.—Figures 6 and 7 show the tongue of a patient with vitamin B_{12} deficiency before and after treatment with vitamin B_{12}. Figure 6, taken before treatment, shows the redness and swelling of his tongue and cheilosis. The area of low-grade infection at the side of his tongue was caused by trauma which resulted from his biting his swollen tongue. On this occasion he was treated with vitamin B_{12} and intrinsic factor orally. As shown in figure 7, taken three weeks later, his tongue was no longer thick and red, the papillae had regenerated, the area of low-grade infection had disappeared, and the cheilosis had almost healed. On a previous occasion we had treated him with liver extract intramuscularly and on another occasion with vitamin B_{12} administered intramuscularly. The response of the tissues was the same in each instance.

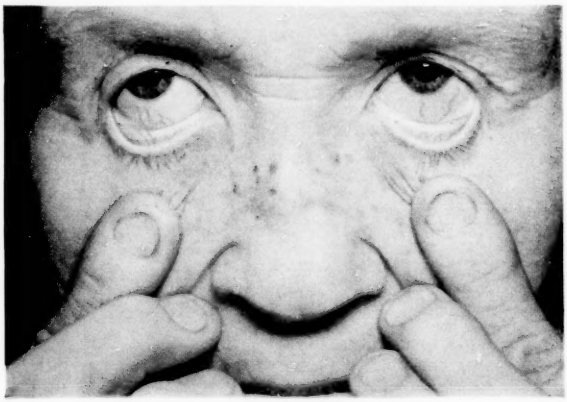

Fig. 4 (case 4).—Face and nails of woman with iron deficiency.

Just as figures 6 and 7 show the typical response of glossitis caused by a deficiency of vitamin B_{12}, figures 8 and 9 show the typical response of glossitis due to folic acid deficiency. The appearance of the

Fig. 5 (case 4).—Nails of woman with iron deficiency.

tongue, the inflamed oral mucous membranes, and the redness at the angles of the mouth were similar to the previous case.

Case 6.—This patient with a typical case of severe macrocytic anemia of "pernicious anemia" type (tropical sprue) in relapse was treated with folic acid by my Latin American associates and me. He was too weak to walk and had to be carried into the hospital, and he was so near death that he could be aroused only with some difficulty. He was mumbling incoherently and refused all food. This particular illness was of several months' duration, although the exact duration was indefinite. Previous attacks of diarrhea had persisted for several weeks, during which time he had had to be cared for by others, and he had been unable to work regularly for several years. Figure 8 illustrates the pallor and sickness of his tongue. At the time this picture was taken his hemoglobin level was only 19%, his red blood cell count was 1,520,000 per cubic millimeter, and the reticulocytes 0.2%. His stools were large, liquid, whitish yellow in color, and foul-smelling. He had megaloblastic arrest of the bone marrow. We gave him 10 mg. of folic acid orally daily. Within 48 hours he began to feel much better. He was mentally alert and sat up in bed and asked for food. Within 96 hours his appetite was voracious and he sat in a chair beside his bed most of the day. On the seventh day of therapy the reticulocytes peaked at 28% and a rapid increase in red blood cells and hemoglobin followed. After six days on therapy his tongue was covered with normal papillae (fig. 9). The frequency and volume of his stools decreased on the third day of therapy. The diarrhea continued to subside, and by the 12th day his stools were normal. After 21 days on therapy his hemoglobin level had increased to 52% and his red blood cell count to 2,790,000. By this time he had gained 12 lb. (5.4 kg.) in body weight. At the time he was discharged he was given instructions in regard to a proper diet, and in the following six months he gained 50 lb. (22.7 kg.) in body weight. He has remained well and has worked steadily.

It is important to realize that this patient would have responded in an identical manner had he been given injections of vitamin B_{12}.

Case 7.—Figure 10 is shown because this woman with typical pellagrous glossitis never developed pellagrous skin lesions. In addition to the glossitis, she also developed a psychosis. Some physicians do not understand pellagra *sine* pellagra, and, having in mind the criteria that pellagra should be associated with dermatitis, the physicians previously concerned with this case did not make the diagnosis of pellagra when no dermatitis was present or did not appear, with the result that she became steadily weaker. The severity of the psychosis increased to the point that her family was considering having her committed to an institution. After treatment with 50 mg. of nicotinic acid orally 10 times daily, the glossitis was relieved and her mental disturbances disappeared. She was given advice in regard to a proper diet, and soon she was able to do her housework and take care of her family.

Many of our talented teachers in the field of nutrition who have had relatively little experience in combating widespread endemic dietary deficiency disorders believe and teach that these deficiency syndromes are due to the lack of a specific nutrient and can be quickly overcome by the administration of that specific nutrient. Working many years in direct daily contact with the problem has taught us that dietary deficiency disorders arising from a lack of the vitamin B complex do not occur

Fig. 6 (case 3).—Tongue of patient with vitamin B_{12} deficiency before treatment with vitamin B_{12}.

singly but as mixed deficiency diseases.[2] The pattern of these disorders is different from person to person and even among individual members of the same family who may eat at the same table. There

is such extreme variability in the presenting symptoms and in the secondary and even tertiary lesions which arise that many years ago we advocated mixed vitamin therapy for treatment and for prevention. This has been extremely effective, except in areas where the teaching is so strongly in favor of giving a single nutrient. In such instances, rather atypical lesions, such as shown here, frequently are not recognized for what they really are and often the nutrient needed to correct the deficiency is not given and the results for the patient and for the physician are most unsatisfactory.

The purpose in showing these lesions which tend to be more easily diagnosed than the average and less complicated in their clinical manifestations is to stress the point that one's working hypothesis, however scientific, is not successful in bringing about gratifying results unless the damaged tissues of the sick person receive the essential nutrients needed to restore them. At the present time in the practice of medicine in the United States, vitamins are much more appreciated and accepted than they were some years ago. Patients receive them in large amounts, with the result that the physician seldom sees lesions such as these we described. This has been one of the great advances in vitamin therapy. It has been gratifying to see that a vast group of practitioners who a few years ago were using these essential nutrients for the treatment of specific disease states are now using them to maintain health, strength, and vigor.

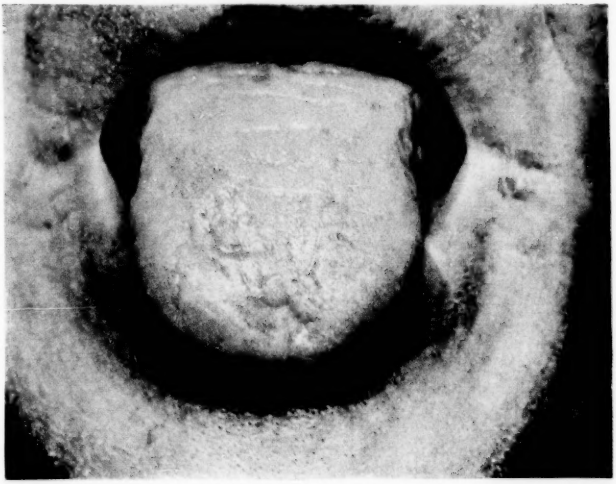

Fig. 7 (case 5).—Tongue of patient with vitamin B_{12} deficiency after treatment with vitamin B_{12}.

Adequate Nutrition During Growth Period

For 30 years I have been interested in the importance of nutrition in the health of the individual, beginning with conception and ending with death. For nearly 20 years we have been studying intensively the insidious effects of sustained substandard nutrition, the so-called hidden hunger, on the growth of infants and children.[3] Our working hypothesis has been that the events of the growth period may determine to a considerable extent a person's subsequent health. (In our experience gross changes certainly affect the health for a long period of time.) The so-called subclinical changes are subtle and their detection requires unusually sensitive methods.

One of our studies of approximately 1,000 undernourished children indicates that the following stigmas are interrelated with the process of human nutritive and growth failure: (1) tortuous, erratic growth curves which lead to a failure to attain expected weight and height; (2) repeated episodes of retarded growth which follow a seasonal pattern recurring every spring and summer; (3) early onset of measurable growth failure such that a significant lag is present by 3 years of age; (4) slow rate of skeletal maturation; (5) high degree of asymmetry in the development of component parts of the skeleton; (6) high frequency and variety of anomalous bone centers; (7) persistence of radiopaque transverse lines in the shafts of the long bones indicative of disturbed bone metabolism; and (8) delayed appearance of postnatal ossification centers and fusion of epiphyses with shafts.

Our goal then is to determine the optimal conditions of the growth of a child so that he attains his maximum physical and mental development. Of all the factors which influence growth, none is more restrictive than time. As physicians know, time sets the limit within which physical growth must be completed. The time allotted for growth, though, may vary from child to child, but any growth debt which may have accumulated prior to the fusion of the epiphyses and diaphyses of the major long bones must be removed if maximum physical development dictated by his inherent growth pattern is to be achieved.

Maximum physical development reflects maximum performance at the cellular, tissue, and organ level. The body processes are so integrated and so dependent upon an adequate supply of essential chemical substances contained in foods that an

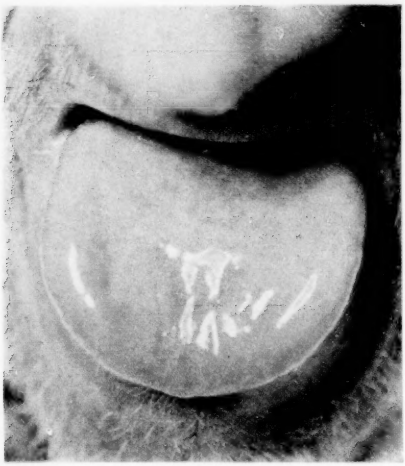

Fig. 8 (case 6).—Glossitis due to folic acid deficiency, before folic acid therapy.

absence or deficiency of any one important factor may impair the efficiency of a whole chain of reactions, each of which affects the health of the child. For example, in our studies dealing with the growth-promoting properties of various supplements in children with nutritive failure, we noted that growth of these children was, in general, accelerated by a proper supplement. Let us see how this works by presenting a brief summary of a representative case of nutritive failure in a child.

Case 8.—A 7-year-old boy was brought to the Nutrition Clinic of the Hillman Hospital by his mother in October, 1953, because "he isn't growing properly." The family history brought out that the father was the only wage earner and worked irregularly making and sacking charcoal, a trade he learned from his father and which he, in turn, was teaching his sons. The mother was industrious as far as her health allowed and she had a clean home and a small garden. There was no evidence of familial disease.

He was the second of four children in a family of three boys and one girl. He was delivered at term and weighed 9 lb. 11 oz. (4,394 Gm.) at birth. He was breast-fed for one month and then given a formula. Solid foods were started at 15 months of age. Orange juice was given frequently beginning at one month of age; cod liver oil was not offered. He sat alone at 4 months of age; he cut his first tooth, walked, and talked at one year of age. He had the usual childhood illnesses and, in addition, from time to time had "trouble with his skin."

The physical examination made just prior to supplementation showed a fairly well-developed, somewhat undernourished boy with a protuberant abdomen. Except for slight scarring at the angles of the mouth and enlargement of the tonsils, no abnormal physical findings were demonstrated. The regular laboratory determinations were negative. Roentgenograms of the left hand and wrist taken every six months showed an increasing retardation in skeletal maturation. His diet, which was studied frequently, showed that his food intake was relatively high in carbohydrates and refined fats and low in protein, calcium, thiamine, nicotinic acid, and calories.

After three years of intensive study, we selected him to receive a dietary supplement of reconstituted nonfat dry milk six days a week for six months, since we had adequately determined that he had chronic nutritional deprivation and increased lag in developmental and skeletal age. At the time of his selection he had a lag of 4 months in developmental age (Wetzel) and of 22 months in skeletal age (Todd).[1]

In addition to his regular diet during the six-month period of supplementation, he was given 6 oz. of Carnation Instant Nonfat Dry Milk Solids daily. This amount was arbitrarily chosen because its nutritional value equals approximately two quarts of skim milk (we mixed it with only 10 oz. of water because we knew his stomach was not large). It was prepared daily in our laboratory and given by one of our workers who recorded his intake. He could and did take each feeding well. In fact, his mother volunteered "he likes it so much he always drinks all of it." This boy is one of a series of children to whom we have given the Carnation Instant milk product. We were interested in testing this new product when we learned that it had been altered to make it instantly soluble in cold water, and that its acceptability over other products available at the time was increased. Naturally, as investigators, we wished to learn if the changes which increased the solubility and palatability had so altered the milk that it would not relieve the underlying general nutritive failure. We wished to know how this milk would affect the children when given as a supplement to their basic

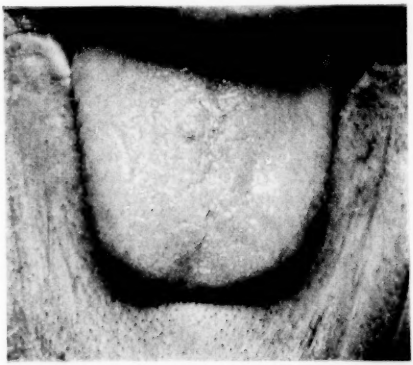

Fig. 9 (case 6).—Typical response of glossitis due to folic acid deficiency, after folic acid therapy.

diets. Since we did not wish to depend on published reports, we chose to make complete chemical and biological assays. Our results are very similar to those published.

This boy's response, like that of the others in the series, has been spectacular. Six months after supplementation was initiated, his lag in developmental age had been reduced

50% and his lag in skeletal age had been reduced over 60%. As can be seen in figure 11, he had been growing rather slowly but with the supplement his growth rate was tremendously accelerated, which, of course, accounts for his paying so much of his "debt" in the short period of six months. If you think this is remarkable, you should see how

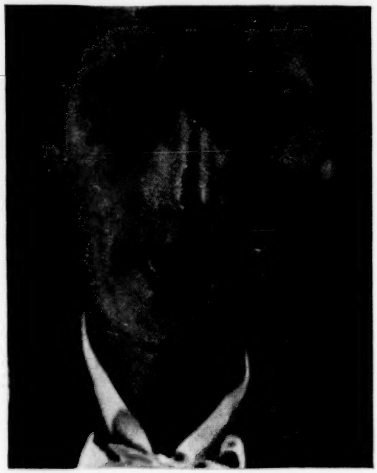

Fig. 10 (case 7).—Woman with typical pellagrous glossitis, without pellagrous skin lesions.

his general physical status and performance improved. Instead of being "fractious" and unwilling to play with other children, he became very much one of the group. His teacher stated "he changed from a surly, backward pupil to one who is responsive and interested in his schoolwork."

For almost a generation now we have recognized that, when diets of an area are deficient in the nutrients essential for life, the response is a general biological blight affecting people and animals. Accordingly, it was decided to test further the biological response to this particular milk preparation by feeding the nutritional equivalent of the diet consumed by the patient in case 8 to each of 30 male, albino, Sprague-Dawley rats. The test diet was based on the results of analysis of repeated diet histories obtained over a three-year period which immediately preceded the selection of this patient for supplementation. The diet contained 18% lard, 19% granulated white sugar, 35% enriched, degerminated white corn meal, and 28% enriched white wheat flour. Each rat was given this diet ad libitum for a period of 20 weeks beginning at 6 weeks of age. Each was killed, autopsy was performed, and histological studies were done. Each rat was compared with its counterpart from a group of the same age, sex, and strain maintained on the test diet supplemented with Carnation Instant Nonfat Dry Milk Solids.

The test diet without the supplement exerted a striking retarding influence on the somatic, sexual, and skeletal growth of the young white rats. The effect on somatic growth is shown in figure 12. Although both rats were the same age, the larger rat, representative of the group on the test diet plus supplement, weighed 419 Gm., whereas the smaller rat, representative of the group on the test diet alone, weighed only 125 Gm. The gross and microscopic manifestations of retarded sexual growth of those receiving only the test diet are illustrated in figures 13 and 14. Each of the rats given only the test diet had testicular atrophy, arrested spermatogenesis, and priapism, whereas none of the group receiving the supplement showed these changes. The inability of the test diet to support proper bone growth is seen in figure 15. In the rat given the supplemented diet the distal metaphysis of the radius is undergoing the sequential conversion of growth cartilage into bone, whereas the rat on just the test diet shows the typical cessation of chondrogenesis and osteogenesis noted in this group. The nutritionally deficient character of the test diet was

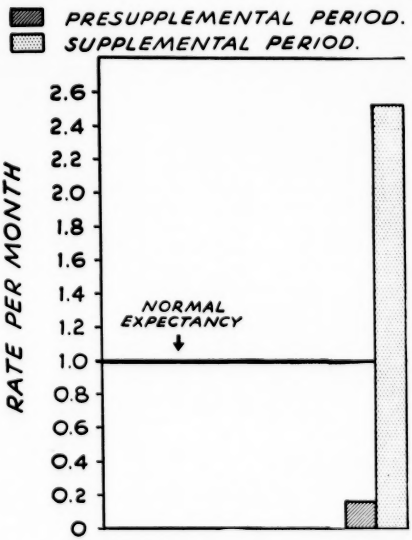

Fig. 11 (case 8).—Contrast between growth rates (Todd) during presupplemental period and supplemental period.

demonstrated not only by its failure to support growth in the young rats but by the great prevalence of deficiency lesions of varying degrees of severity which were encountered in these animals.

Specifically these included fatty liver (fig. 16), dacryohemorrhea (bloody tears) (fig. 17), dry, coarse hair, alopecia, and dermatitis.

For many years we have been relating nutrition directly or indirectly to nearly all the diseases and ills of man. We hope that certain observations

Fig. 12.—Small rat, restricted to deficient diet eaten by child in case 8, contrasted to larger rat, a litter mate which was given test diet plus milk supplement.

which we have made on children will serve as the groundwork for a complete chemical evaluation of the human growth process. At present we have only a thread of the information necessary for an understanding of the complex process of the growth and development of children.

Claude Bernard emphasized that the living person must be treated as a harmonious whole. It is interesting that the growth of many of our organ systems can proceed at different rates and yet be normal. Nevertheless, there is an underlying orderliness of these processes, and it is with the measurement of some of these processes that we are directly or indirectly concerned. Let us give an example of an entirely different medical problem and its effect on the health of the child.

Case 9.—A 22-year-old white female was brought by her mother to the Nutrition Clinic of the Hillman Hospital when she was 7 years of age. The mother, who had been treated in the Nutrition Clinic for pellagra and other deficiency diseases, was concerned about her daughter's health. She said that the child was "well nourished but she doesn't eat well and is nervous and doesn't feel like playing with the other children." She appeared to be extremely anxious and hypersensitive. There was typical pellagrous dermatitis around both ankles. The child was treated properly and responded well. We decided to study her growth progress, and thereafter measurements, radiographs, and dietary assessments were made at regular intervals. In June, 1943, when she was 8 years 2 months of age, she contracted typhoid. She was confined to bed for four weeks during which time she lost weight. We made certain, however, that she continued to eat properly and that she received ample vitamin supplements during this period of time.

People observing her were impressed with the fact that she recovered without serious complications; however, we had long been studying the effects of infectious processes, such as tonsillitis, appendicitis, and childhood diseases, on the metabolic processes of the body and knew that the prognosis was good. In our lectures we have always stressed that the metabolism of the body is never static, that the nutrients tend to ebb and flow, so to us the effect on her bone and over-all body growth, as indicated by general measurements and plotting on the Wetzel grid (fig. 18), was not surprising. As can be seen in figure 19, the effect on the bone was reflected by the deposition of a heavy transverse radiopaque line in the distal end of the shaft of the radius which required more than three years to disappear completely. The channel and auxodrome curves on the Wetzel grid were characterized by abrupt declines coincident with the period of illness. The preinfection points were reattained nine months after the onset of the disease.

This case demonstrates the sensitivity of a child's growth to an acute infectious process. We know from the study of literally thousands of cases that unless the food intake is quantitatively and qualitatively sufficient to remove the growth debt incurred by the disturbed nutrition and metabolism accompanying an illness, as well as to provide the wherewithal for normal body increment, the child will never achieve his maximum growth potential.

Nutrition in Adult with Acute or Chronic Disease

So much for a glimpse of the effect of disease on the nutritional status of the young and growing person. Now let us turn for a moment to a brief discussion of the relation of proper nutrition to

Fig. 13.—*Left*, priapism in rat fed only deficient diet; *right*, rat fed same diet plus milk supplement.

the mature person who develops acute or chronic disease. In my opinion, all severe disease processes affect the metabolism of the tissues and, therefore, the nutrition of the tissues, but arbitrarily I shall select rheumatoid arthritis to discuss with you in order to present a way of thought. As physicians,

you know that "rheumatism" is the great crippler, yet it kills relatively few. In the United States the number of persons afflicted with "rheumatism" is greater than the total number of persons with heart disease, cancer, poliomyelitis, diabetes mellitus, and

Fig. 14.—Photomicrographs (same magnification in each) of sections of rat testes. *Left*, from rat fed test diet; *right*, from rat given test diet plus milk supplement. Note spermatogenesis in rat given supplement and its absence in rat fed only test diet.

tuberculosis. One of the projects on which we have worked is how to devise methods of keeping people with rheumatic disorders on the job.

In the course of investigating new therapeutic agents or devising new methods to use old therapeutic agents, we carefully study their effects on the nutritional status of the patient. The proper use of these therapeutic agents and foods may mean the difference between a useful life and a useless life, between a long life and an early death. Accordingly, the responsibility of the physician is overwhelming. A number of times we have published our observations on the striking decrease in toxicity from disease and increase in food intake after the administration of pituitary ACTH, cortisone, or one of the related steroids to persons with rheumatic disorders.[3] Since the salicylates also are very effective therapeutic agents in many persons with such disorders, from a nutritional point of view it seemed important to check their effect singly and in combination with antiarthritic steroids (cortisone, hydrocortisone, methylprednisolone [Medrol], prednisolone, prednisone, and triamcinolone [Aristocort]). In properly selected patients the salicylates or the salicylates and the antiarthritic steroids have had a profound beneficial effect characterized by the prompt amelioration of the pain, stiffness, and swelling. None of these agents are specific in their therapeutic effect, and at termination of treatment there frequently is recurrence of pain, tenderness, and stiffness. For the moment let us not consider the usual symptoms associated with rheumatic disorders but let us think of the nutritive status of people who have these conditions. We find that they may be obese and actually need a calorie reduction, though many of those who are obese may be deficient in proteins and vitamins. Many are generally undernourished and, of course, need the best possible diet. Some have typical deficiency disorders and, in order to rehabilitate them, these deficiency states have to be treated. There are many more who have a mild degree of nutritive failure.

Many rheumatologists now look for nutritive failure among the patients who have arthritis and other debilitating diseases. Aspirin alone or aspirin

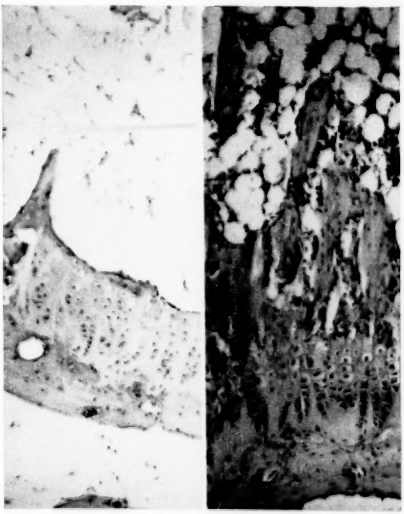

Fig. 15.—Bone sections from rats from same litter. *Left*, poor bone development in rat fed only test diet; *right*, normal bone development in rat fed this diet plus milk supplement.

with a small amount of one of the steroids, as we have shown, plays an important role in the nutrition of patients (fig. 20). Many of these patients are

Specifically these included fatty liver (fig. 16), dacryohemorrhea (bloody tears) (fig. 17), dry, coarse hair, alopecia, and dermatitis.

For many years we have been relating nutrition directly or indirectly to nearly all the diseases and ills of man. We hope that certain observations

Fig. 12.—Small rat, restricted to deficient diet eaten by child in case 8, contrasted to larger rat, a litter mate which was given test diet plus milk supplement.

which we have made on children will serve as the groundwork for a complete chemical evaluation of the human growth process. At present we have only a thread of the information necessary for an understanding of the complex process of the growth and development of children.

Claude Bernard emphasized that the living person must be treated as a harmonious whole. It is interesting that the growth of many of our organ systems can proceed at different rates and yet be normal. Nevertheless, there is an underlying orderliness of these processes, and it is with the measurement of some of these processes that we are directly or indirectly concerned. Let us give an example of an entirely different medical problem and its effect on the health of the child.

Case 9.—A 22-year-old white female was brought by her mother to the Nutrition Clinic of the Hillman Hospital when she was 7 years of age. The mother, who had been treated in the Nutrition Clinic for pellagra and other deficiency diseases, was concerned about her daughter's health. She said that the child was "well nourished but she doesn't eat well and is nervous and doesn't feel like playing with the other children." She appeared to be extremely anxious and hypersensitive. There was typical pellagrous dermatitis around both ankles. The child was treated properly and responded well. We decided to study her growth progress, and thereafter measurements, radiographs, and dietary assessments were made at regular intervals. In June, 1943, when she was 8 years 2 months of age, she contracted typhoid. She was confined to bed for four weeks during which time she lost weight. We made certain, however, that she continued to eat properly and that she received ample vitamin supplements during this period of time.

People observing her were impressed with the fact that she recovered without serious complications; however, we had long been studying the effects of infectious processes, such as tonsillitis, appendicitis, and childhood diseases, on the metabolic processes of the body and knew that the prognosis was good. In our lectures we have always stressed that the metabolism of the body is never static, that the nutrients tend to ebb and flow, so to us the effect on her bone and over-all body growth, as indicated by general measurements and plotting on the Wetzel grid (fig. 18), was not surprising. As can be seen in figure 19, the effect on the bone was reflected by the deposition of a heavy transverse radiopaque line in the distal end of the shaft of the radius which required more than three years to disappear completely. The channel and auxodrome curves on the Wetzel grid were characterized by abrupt declines coincident with the period of illness. The preinfection points were reattained nine months after the onset of the disease.

This case demonstrates the sensitivity of a child's growth to an acute infectious process. We know from the study of literally thousands of cases that unless the food intake is quantitatively and qualitatively sufficient to remove the growth debt incurred by the disturbed nutrition and metabolism accompanying an illness, as well as to provide the wherewithal for normal body increment, the child will never achieve his maximum growth potential.

Nutrition in Adult with Acute or Chronic Disease

So much for a glimpse of the effect of disease on the nutritional status of the young and growing person. Now let us turn for a moment to a brief discussion of the relation of proper nutrition to

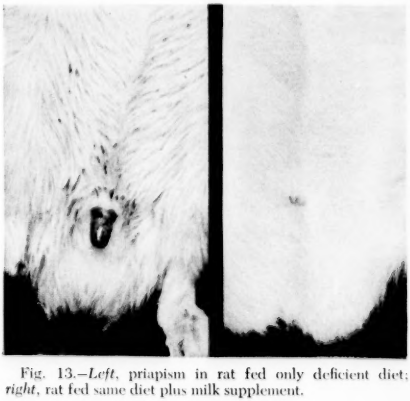

Fig. 13.—*Left*, priapism in rat fed only deficient diet; *right*, rat fed same diet plus milk supplement.

the mature person who develops acute or chronic disease. In my opinion, all severe disease processes affect the metabolism of the tissues and, therefore, the nutrition of the tissues, but arbitrarily I shall select rheumatoid arthritis to discuss with you in order to present a way of thought. As physicians,

you know that "rheumatism" is the great crippler, yet it kills relatively few. In the United States the number of persons afflicted with "rheumatism" is greater than the total number of persons with heart disease, cancer, poliomyelitis, diabetes mellitus, and

Fig. 14.—Photomicrographs (same magnification in each) of sections of rat testes. *Left*, from rat fed test diet; *right*, from rat given test diet plus milk supplement. Note spermatogenesis in rat given supplement and its absence in rat fed only test diet.

tuberculosis. One of the projects on which we have worked is how to devise methods of keeping people with rheumatic disorders on the job.

In the course of investigating new therapeutic agents or devising new methods to use old therapeutic agents, we carefully study their effects on the nutritional status of the patient. The proper use of these therapeutic agents and foods may mean the difference between a useful life and a useless life, between a long life and an early death. Accordingly, the responsibility of the physician is overwhelming. A number of times we have published our observations on the striking decrease in toxicity from disease and increase in food intake after the administration of pituitary ACTH, cortisone, or one of the related steroids to persons with rheumatic disorders.[5] Since the salicylates also are very effective therapeutic agents in many persons with such disorders, from a nutritional point of view it seemed important to check their effect singly and in combination with antiarthritic steroids (cortisone, hydrocortisone, methylprednisolone [Medrol], prednisolone, prednisone, and triamcinolone [Aristocort]). In properly selected patients the salicylates or the salicylates and the antiarthritic steroids have had a profound beneficial effect characterized by the prompt amelioration of the pain, stiffness, and swelling. None of these agents are specific in their therapeutic effect, and at termination of treatment there frequently is recurrence of pain, tenderness, and stiffness. For the moment let us not consider the usual symptoms associated with rheumatic disorders but let us think of the nutritive status of people who have these conditions. We find that they may be obese and actually need a calorie reduction, though many of those who are obese may be deficient in proteins and vitamins. Many are generally undernourished and, of course, need the best possible diet. Some have typical deficiency disorders and, in order to rehabilitate them, these deficiency states have to be treated. There are many more who have a mild degree of nutritive failure.

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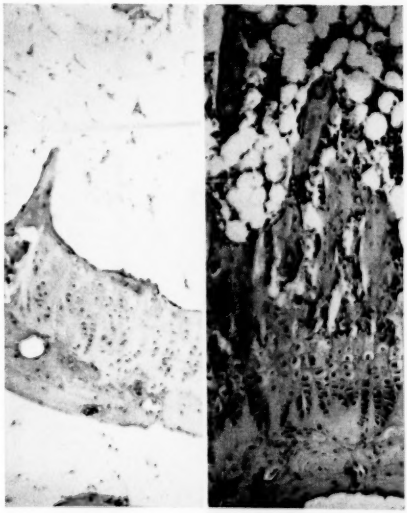

Fig. 15.—Bone sections from rats from same litter. *Left*, poor bone development in rat fed only test diet; *right*, normal bone development in rat fed this diet plus milk supplement.

with a small amount of one of the steroids, as we have shown, plays an important role in the nutrition of patients (fig. 20). Many of these patients are

so depressed that their morale is low and they lose their desire to eat. Some of them are actually so incapacitated that they cannot earn money to purchase food. Many who have food will not eat, and some cannot eat because the arthritis affects the

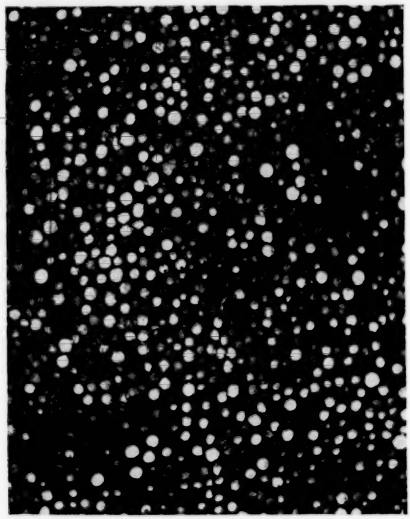

Fig. 16.—Section of fatty liver from rat on test diet.

joints of the jaws so they cannot even open their mouths. Others have nausea and vomiting, with the result that absorption is decreased. An example of one facet of the relation between disease and inadequate nutrition is demonstrated by the following brief case history.

Case 10.—A 60-year-old white worker was sent to the Nutrition Clinic of the Hillman Hospital in an ambulance in 1950. We found his joints swollen and the muscles and joints excruciatingly painful. He was unable to walk or even stand alone, and it was obvious that he was severely ill. His temperature ranged from 101 to 105 F (38.3 to 40.5 C).

Later we learned that when he was a small boy his legs ached a great deal, and during the winter months they ached until he "felt they would bust." His mother gave him relief by warming a flannel blanket and wrapping his legs in it. Fifteen or 20 years prior to 1950 he had some pain and swelling of the ankles on a few occasions. This was not very severe and disappeared when a "pharmacist" gave him a liniment which he rubbed on them. When questioned about aspirin or any medication by mouth, he said he had not taken aspirin because he thought that it was only for headaches and that "it might be dangerous."

Three weeks prior to the time we first saw him, he suddenly developed acute pain in his left foot and ankle which soon spread to all his joints. He stated that each day the joints became "hotter," more swollen, and more tender. The pain could not be controlled by codeine or morphine so that any movement caused him unbearable pain and he could not refrain from crying out. He lost his desire for all foods and "just lived on coffee." He knew that he had lost several pounds in body weight, although he did not know exactly what his weight loss was. He was admitted to a hospital and given injections of penicillin and morphine. He did not improve and was referred to our clinic by his physician.

When we first saw him, his temperature was 101 F. The physical findings were negative except for general weakness, great swelling of his ankles, and tenderness all over his body. His erythrocyte sedimentation rate was 59 mm. per hour (corrected). A diagnosis of acute "rheumatism" was made, and he was given large doses of cortisone and aspirin. We decided to allow him to go home. He was advised to move about as much as possible, and he and his wife were instructed in regard to his treatment, diet, and general care. Within 24 hours after therapy was started he volunteered that he had obtained great relief; four days later he got out of bed, made coffee for himself and his wife, and ate a big breakfast. This was the first time in many days that he had been able to get out of bed or to eat. On the fourth day of therapy his temperature was normal. After 22 days of treatment at home there was no limitation of movement of any of his joints, all the pain and swelling had disappeared, and he walked without difficulty. He said, "I feel so good I want to get back on the job. I'm eating so much I'll get fat if I don't work it off." He returned to work and has not missed a day since. At times he has had some aching in his ankles, hands, and shoulders and swelling of his ankles and hands. In every instance the recurrence of these symptoms was associated with a lack of desire for food. Prompt relief followed the administration of three to four 5-grain (0.3-Gm.) aspirin tablets every four to six hours, except on four occasions when this did not prove to be, in his own words, "strong enough." On three of these occasions we gave him the same amount of aspirin in the form of "Cordex," a preparation which also contains prednisolone. This material has been "strong enough" to give him prompt relief of pain which is associated with a return of his desire for food and a decrease in the swelling of his joints (fig. 21). On the occasion of the fourth relapse we gave him a mixture of aspirin (the same amount as mentioned above) and prednisone. The administration of this preparation called Co-Deltra was also followed by prompt relief of symptoms and an increase in desire to eat.

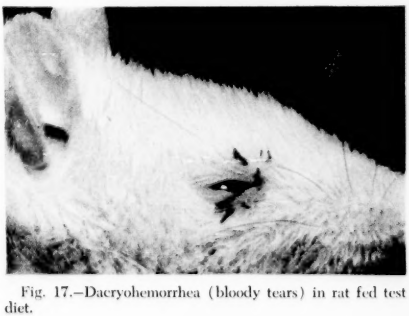

Fig. 17.—Dacryohemorrhea (bloody tears) in rat fed test diet.

This case is representative of patients with acute or chronic disease in which the disease and the pain are such that they do not eat properly. When the disease is brought under control, they do eat. We have shown how the intensity of the disease

varies and also how this patient's job was saved for him by prompt therapy. In the past seven years he has maintained his nutritional status, strength, and vigor and has been able to work every day with a minimum of treatment.

The majority of persons with severe rheumatic disorders are more difficult to treat than this patient because their disease lingers on day after day and it is a problem to get them to eat properly. It can be done, however, by individual attention, by prescribing proper mixtures of vitamins when indicated, and by giving adequate amounts of salicylates alone or combined with steroids. The importance of eating a proper diet must constantly be pointed out to the patient. Over and over again we have seen persons with acute or chronic disease develop coexisting nutritional disorders.

The response of patients with megaloblastic anemia to cortisone, hydrocortisone, prednisolone, and prednisone has been described by our group from time to time.[9] The initial fall of the serum-iron level, which is always seen early in the successful treatment with vitamin B_{12} or folic acid, is not observed with these steroids. These patients have a satisfactory clinical and hemopoietic response and an increase in reticulocytes followed by an increase in red blood cells and hemoglobin. This response, if enough material is given, follows through until the bone marrow is restored to a normoblastic state. My associates and I have shown recently that triamcinolone and methylprednisolone produce similar results. All six of these steroids were given by mouth.

We do not recommend these materials for the treatment of any form of megaloblastic anemia that will respond to vitamin or nutritional therapy. The precise roles of folic acid and vitamin B_{12} in converting megaloblastic to normoblastic bone marrow is not understood, and the role of the steroids is still less understood. Some of the hematologists and rheumatologists, who certainly would wish to treat their "rheumatics" nutritionally when necessary, should have drawn to their attention the danger of suppressing unsuspected megaloblastic anemia in their patients. Is it not remarkable that these substances which relieve inflammatory reactions, allergic reactions, and so forth can stimulate hemopoiesis under certain circumstances? While they

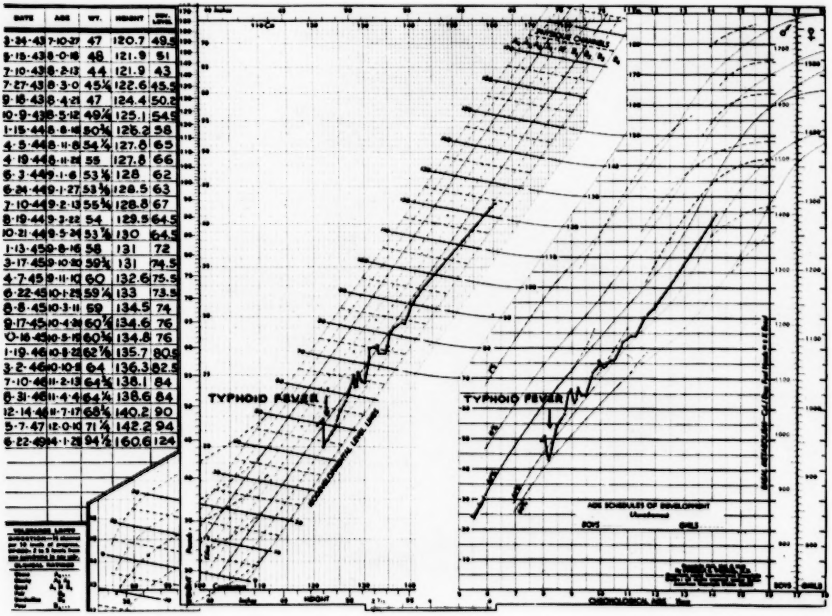

Fig. 18.—Grid for evaluating physical fitness in terms of physique (body build), developmental level, and basal metabolism—a guide to individual progress from infancy to maturity.

suppress arthritis or allergy, for example, they may also produce blood regeneration; yet there still would be a fundamental lack of essential nutrients in the tissues. There is no reason to think that the steroids relieve acute combined degeneration of the spinal cord. It behooves the physician treating chronic diseases to insure proper and complete nutrition for his patients. Millions of persons who have these disorders demand and deserve our help, as do the millions who have minor aches and pains.

The study of minor aches and pains is a difficult task. The breadth of the field, the lack of clearly defined disease manifestations and mechanisms, and almost complete lack of leads makes the medical approach difficult. We find that many persons with minor aches and pains sum up their problem by saying that they have not had any fun in years and that they can barely drag themselves around. They have vague joint pains, and perhaps even more difficult to endure is their great fatigue. Because of the vague nature of their complaints, such as "nervousness," "forgetfulness," "I'm all worn out," "aching in my joints and muscles," they often are called neurotics and usually considered nuisances. Most of them have had long-continued treatment of one sort or another which has failed to give them relief and they become frustrated in their search for relief.

Still speaking of minor aches and pains, we know that as we become older we experience a multitude of little maladies, which often persist or disappear only to recur again and again. They constitute no serious threat to life, yet they are annoying and may handicap. Frequently these minor disorders are precursors of more disastrous impairment. In many persons they become the basis of an anxiety state. Most of these anxieties are needless. Muscle cramps, aching of the joints, and innumerable symptoms are experienced by virtually every person at one time or another. The circumstances under which they occur are benign. The same symptoms may appear in association with a wide range of underlying disturbances, some of which are transient while others are ominous. There are many clinical descriptions of odd and localized symptoms, particularly in older persons who have an impoverished blood supply. The disturbance of the underlying mechanisms is not understood. The facts are meager and there is much obscurity surrounding all of them. There is much guessing and much concern about such complaints.

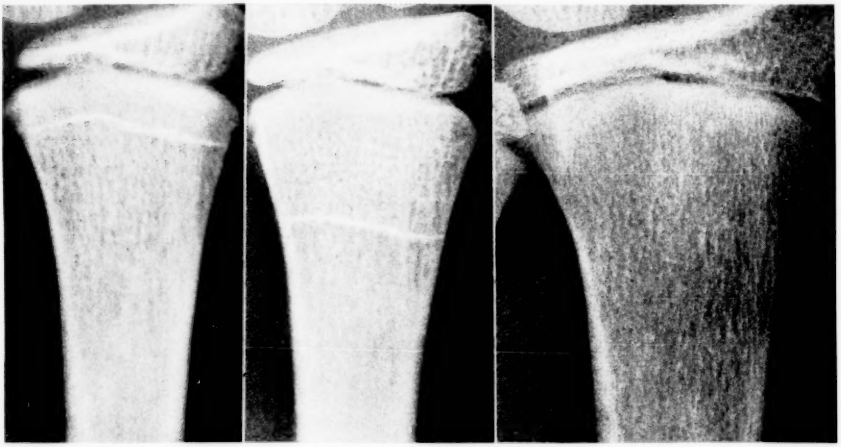

Fig. 19.—*Left*, transverse radiopaque line caused by interference with nutrition of patient in case 9 at time she had typhoid. As bone increased in length, transverse line became farther removed from joint surface *(center)*. Eventually, line disappeared *(right)*. This is the orderly sequence of events that each such scar goes through.

Our group is trying to devise methods for the better management of these problems. We have given temporary and transient relief to hundreds of persons by administering aspirin and, in some instances, steroid and aspirin mixtures, with the result that many of them have resumed much more active function. As a time-honored procedure, patients have rubbed liniments on their afflicted muscles and joints. We chose to study one, Intracel, (topically applied pain killer containing salicylamide benzocaine, and 46% isopropyl alcohol) to

see if we could work out the mechanism of action. We are still working on it. Many patients think they get relief. After the rubbing of this material on a patient, we have demonstrated that salicylates are excreted into the urine, but we have not been able to show a clear-cut cause and effect relationship between the absorption of the salicylate and the relief of symptoms oftentimes experienced by the patient.[6a] It would seem that better studies of the remedies that patients find helpful should be devised.

For ever so long many physicians have given primary attention to the terminal stages of chronic disease. Yet, it is in the early stages that the physician can do so much. Before we can make great strides, those of us doing investigation will be required to make painstaking biochemical, physiological, and pathological studies that will lead to better diagnostic measures and therapeutic remedies. In the meantime, the practicing physician should be concerned in relieving his patients, in preventing the sequelae, and in keeping them contented and at work. He must treat the patient rather than the disease. Every patient with an anxiety state, disability, or symptom, no matter how "minor," offers a challenge to the physician.

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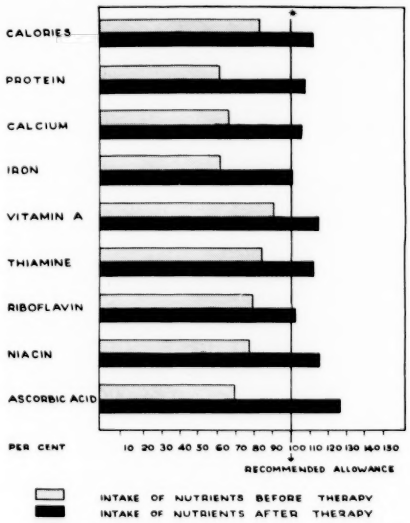


Fig. 20.—Comparative intake of nutrients before and after therapy with prednisolone and aspirin in patient with rheumatoid arthritis. Asterisk indicates allowance recommended by Council on Foods and Nutrition, National Research Council.

Effects of Malnutrition and Undernutrition on Nervous System

We all know that mental illness is a major medical problem. I wish to discuss briefly with you some of the effects of malnutrition and undernutrition on the nervous system. Think of the loss of creativeness and productivity caused by this type of illness alone! Who can estimate its cost in terms of human misery?

In the past, mental illness has been considered a social, moral, or legal problem. To me, the medical profession has the responsibility of treating patients who are mentally diseased, and of preventing mental illness. As physicians, we all know that mental disorders may be an alteration of social behavior, an abnormal emotional response, a neurosis, or a psychosis. The patient may be slightly incapacitated or he may be stricken with a major psychosis that makes hospitalization necessary. It is well to remember that mental disorders are prevalent wherever human beings exist.

Some of the custodial institutions for mental diseases are doing better and better work, but I sometimes wonder if others should not be called "containers of sick people" or "storehouses of sick people." At any rate, the problem is great. Ever since insane asylums have existed, the pellagrin has been pushed into them. These patients were not recognized as pellagrins. Usually the diagnosis was "psychogenic" psychosis. They may have been mistaken for a "schizophrenic," a "manic depressive," or some other classified type of psychosis. Having trained myself more as a nutritionist than as a psychiatrist, I was more impressed by the prolonged dietary deficiency of these patients than by their psychic alteration. Eventually my associates and I found that a lack of niacin in their diets allowed the mental symptoms to arise.[7] After its administration, these symptoms disappeared. Thus we showed that the relief of one particular kind of undernutrition or malnutrition could produce complete relief of mental symptoms. Until this time pellagra was viewed as a mental illness practically incurable. Thanks to the recommendation by the American physician of widespread use of niacin, the disease has practically disappeared.

My associates and I are now in the process of making a 20-year appraisal of niacin as a therapeutic agent. An effect on the second generation is already apparent and can be visualized by means of the following brief case history of a mother and her daughter.

Case 11.—The mother was born in north central Alabama and was of Anglo-Saxon stock. She married a hard-working young man who also was of Anglo-Saxon extraction, and they were in good circumstances until the "depression" closed the coal mines in 1929. The husband said, "When the mine shut down, I was thrown out of work." From that time on the diet consisted of corn bread, "fat back," syrup, and occasionally beans or an egg. The wife began losing body weight, and after the birth of each child she found

herself weaker and weaker. In 1933 she began having "pellagracy" each spring. This "breaking out" of the skin appeared on her ankles and forearms and each year it was associated with "nervous crying spells." Her husband said that in 1936 she suddenly "went right out of her mind," and in February of that year she was committed to a mental institution.

Four months after the mother's admission, the above-mentioned child was born. It is this child, literally born in a mental hospital, whom I would like to tell you about now. The mother, who was treated with niacin and a better diet, took this child home, and at an early age this child did some of the housework and, when two younger children were born, helped with them. In time she went to high school, where she was an excellent student, and her teacher stated, "She is talented and very responsible." She graduated from high school and also graduated from the university, where she won a number of competitive scholarships.

Comment.—In summary, certainly the mother could not have been released from the institution without treatment, and it is doubtful that she could have worked hard and continued to have children if she had not had treatment from time to time in her home. But, even more impressive to me is the fact that a baby born in a mental institution was able, through the efforts of her mother and, later, of herself, to win competitive scholarships.

Fig. 21 (case 10).—*Right*, swelling of lower part of leg and ankle before treatment; *left*, same leg after four days of therapy.

The older physicians among you, of course, are well acquainted with the severe mental symptoms of pellagra that manifest themselves in various types of psychoses. Perhaps the most common is that in which loss of memory, disorientation, confusion, and confabulation are predominant. In some types excitement, mania, depression, and delirium predominate. In our experience a paranoid condition is common in pellagrins. These patients, acting on their paranoid delusions, are more active than other pellagrins with psychoses.

After we had learned how to correct the baffling brain changes associated with the severe mental illness of pellagra, we began to grapple with the problem of how to relieve people who had early symptoms only. Soon we learned that many persons who had prolonged dietary deprivation suffered from what was called "hysteria," "anxiety," "extreme nervousness," or "depression." These people disliked bright lights, bright colors, noises, odors once tolerated, and foods once relished. They described themselves as being "jittery," "nervous," "restless," "fractious," and "tense." They stated that they constantly expected something terrible to happen. Still others complained of a poor memory, a memory so poor that they could not remember even what happened 10 minutes before. The patients with the milder afflictions tended to become worse as time went on, and many of them developed personality disorganization.

It is not my intention to delve deeply into why these people could not satisfy their longing for inward peace. I could not accept the concept that their brains were irreparably damaged; it seemed that the cells were waiting listlessly and would function again at full efficiency when we gave them the required nutrients. To make a long story short, we showed that not only niacin was necessary for the integrity of the nervous system but thiamine too. In samples of blood entering and leaving the brain, my associates and I observed a profound alteration in the content of glucose and lactic acid. By studying the oxygen utilization and the lactic acid production, we learned that in patients with vitamin B_1 deficiency and with mental symptoms, the cerebral metabolism was diminished by 60%.[9] These observations afforded a basis for the explanation of our clinical demonstration that thiamine relieved the mental symptoms in a syndrome complex which we termed the initial nervous syndrome. This syndrome can now be prevented with administration of thiamine and niacin. Other vitamins, such as pyridoxine, folic acid, and vitamin B_{12} under certain circumstances may be useful in correcting symptoms arising from the nervous system. Today it is with prevention that you and I, as physicians, are primarily concerned.

Our group long ago learned that the emotional disorders of older people can sometimes be overcome or relieved through the science of nutrition. So many of the older patients have an initial complaint of mental fatigue. They learn that by renewed effort they can adjust, but the process of compensation worries them and anxieties and depression may develop. They feel they are no longer needed, and many of these people have no incentive

for living. They resist changes and their habits become fixed. In many the personality becomes disorganized or rigid and the judgment poor. They lose insight and accept flattery hungrily. Some of them let reality slip away. All too often they confuse manliness and sexual ability. They may develop insomnia and later may become disoriented as to time, place, and, finally, person. It is in this manner that aging brings to them accumulated emotional trauma. All too often the patients have a diagnosis of cerebral arteriosclerosis with psychosis, using age as the only criterion. In trying to aid these people, we assume that their personality is the result of their hereditary factors and their experiences, and that their incapacitation, whether due to a mild neurotic disorder or to a major psychosis, is not necessarily irreversible. Whatever their permanent cerebral incapacity may be remains to be established, but the physician must not accept it without trying to do something for the patient.[65]

Whether among the old or the young, symptoms arise from damaged tissues. In general, we stress that the processes of protection or of repair will be impeded in tissues that are nutritionally deficient. Mere duration of life is not enough. From time to time we have given you examples of the cells being damaged but not being finished. Give them what they need and they will muster strength and come back. We do not have enough information, of course, to know all they need. The science of nutrition has only scratched the surface, but it has made some progress toward a real solution of mental illnesses.

We know that many nutrients are necessary for the integrity of the nervous system. Yet many persons with anxiety and tension states do not have their neuroses relieved by application of any or all of the nutrients now known. Accordingly, it seemed imperative that we study the so-called tranquilizers or ataractic drugs from the viewpoint of their effect on nutrition. This study is still under way, but we can say that there is, under certain circumstances, a loss of nutrients when these drugs are used and that the safest and best way of using them generally is to be certain that there is a platform of solid nutritional therapy instituted to protect the nervous system. The tranquilizing drugs certainly are an effective aid in managing severely disturbed, hospitalized psychotics, but special attention should be given to the nutrition of these patients because some of them can be helped by nutritive methods. In the past 20 years we have relieved many persons of symptoms arising from the nervous system with synthetic vitamins and a good diet. Yet these persons had no clinical evidence on which a definite diagnosis of deficiency disease could be made. On several occasions I have talked with Dr. John T. Ferguson, who is studying this aspect intensively, particularly in older people. It occurred to me that in our clinic we could be of most service in working with the milder afflictions.

The great majority of people with nutritive failure and "functional" mental disorders respond promptly and completely to adequate nutritional therapy, but there are some who have anxiety states that cannot be corrected entirely by nutritive therapy alone and it is with those people that this particular study is concerned. Conversely, some "functional" mental symptoms arising from nutritive disorders are not corrected adequately by giving the tranquilizers alone—that is to say, vitamin therapy does not replace tranquilizers and tranquilizers do not replace vitamin therapy, but, when indicated, they should be used properly together for the benefit of the patient. Obviously we could not study all the tranquilizers so we chose meprobamate (Miltown, Equanil) because it is well tolerated, orally effective, and suited for prolonged therapy. The following brief case history is illustrative of what can be done by the judicious use of vitamin therapy and a mild tranquilizer.

CASE 12.—A 49-year-old white man was first brought to the Nutrition Clinic of the Hillman Hospital in 1940 complaining of weakness, weight loss, photophobia, soreness of the mouth and tongue, pain and burning of the legs and feet, forgetfulness, and depression. Physical examination showed a man with nutritive failure. He had pellagrous glossitis, great dilatation of the conjunctival vessels associated with photophobia and lacrimation, excruciating tenderness in the nerve trunks of his legs, and hyperactive Achilles and patellar reflexes. His diet for many years was composed chiefly of refined carbohydrates and fats. He rarely ate protein in the form of meat, milk, or eggs. In a period of some 10 years he lost 25 lb. (11.3 kg.) in body weight. He was worse in the spring and fall of the year, and, although his course was not steadily downhill, his symptoms were somewhat more severe with each recurrence. Because of the severe pain in his feet and legs and his sleeplessness, he was given an injection of thiamine. Within six hours the pain had disappeared and that night he slept better than he had for a long time. We then decided to give him sterile saline solution as a placebo. The pain in his feet and legs returned within 48 hours and it was not relieved by saline solution. Without his knowledge the saline solution was replaced with thiamine, 10 mg. parenterally twice a day for a week. Again the pain was promptly relieved and he was able to sleep. For the following month he was given by mouth 10 mg. of thiamine daily and 50 mg. of niacin 10 times a day. Within 48 hours after this therapy was started his pellagrous glossitis disappeared, his appetite increased, and his forgetfulness and depression were relieved. The symptoms arising from his eyes were not relieved, and we decided to give him injections of riboflavin, 10 mg. twice a day for a week. The dilatation of the conjunctival vessels, the lacrimation, and the photophobia began to decrease on the second day of therapy, and by the seventh day the eye symptoms were greatly relieved. This patient's diet improved, but it has not always been completely adequate and he has required treatment from time to time. In the fall of 1957 he had influenza, and since then has complained of sleeplessness and a "sick stomach." Thiamine or niacin gave him no relief. It was decided to give him meprobamate, 200 mg. every 12 hours. After five days he volunteered that he was sleeping

much better, and he no longer complained of having a "sick stomach." In the two months that he has been on this therapy he has had no recurrence of these symptoms.

It is important, as can be seen by this case history, to realize that the mere fact a person has nutritional deficiency does not mean that he cannot have other types of disorders also.

Summary and Conclusions

I have discussed with you a few of the many advances which have been made in nutrition in recent years. You have seen that what patients eat has much to do with their health and with their recovery from ill health. Primary or secondary nutritional disorders produce or complicate all the problems of the sick. I have stressed that we should be concerned with the prevention and with the earlier stages of disease when the disturbances are almost imperceptible and that we should not wait until these disturbances bring tremendous burdens and stark tragedies.

In the beginning man's main concern was the obtaining of food. He did not know that bodily functions are impaired when the cells and tissues of the body are deprived of essential nutrients. Of necessity, our ancestors had to obtain all their vitamins and essential nutrients as they were produced by nature. We have learned that, when fruits, vegetables, eggs, milk, fish, meat, and other foods are not available in adequate amounts, or for any reason are not satisfactory, we must recommend methods of maintaining tissue integrity. We have shown how this may be done by supplementing what foods are available with certain synthetics and food concentrates. This means that the goal we are seeking is to devise methods of achieving biochemical independence for people. To do this, we know that excellent nutrition is basic, that disease is chemical in its origin, that the body cells can fight back to an amazing degree, and that our tissues, when properly replenished, can come into their own again. A number of examples are reported of how this works in actual practice. Above all, we must realize that, as physicians, we are properly the guardians of the health and nutrition of our patients, and it is for us to prevent or treat disease so as to increase their vigor, strength, and happiness.

The studies in nutrition were done at the Nutrition Clinic, Hillman Hospital, Birmingham, Ala., at the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago, at the Hospital Mimiya, Santurce, Puerto Rico, and at the General Calixto Garcia Hospital, Havana, Cuba.

This paper is based to a considerable degree on concrete data obtained by the associates of the author working in Alabama, Illinois, Cuba, and Puerto Rico.

References

1. Spies, T. D.: Rehabilitation Through Better Nutrition, University of Cincinnati Studies in Nutrition at Hillman Hospital, Birmingham, Ala., Philadelphia, W. B. Saunders Company, 1947.

2. Spies, T. D.; Hightower, D. P.; and Hubbard, L. H.: Some Recent Advances in Vitamin Therapy, J. A. M. A. **115**:292-297 (July 27) 1940. Spies, T. D.: Diagnosis and Principles of Treatment of Dietary Deficiency Diseases, Texas J. Med. **38**:427-431 (Nov.) 1942.

3. Spies, T. D.; Bean, W. B.; and Stone, R. E.: Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to Vasodilator Action and Effect on Mental Symptoms, J. A. M. A. **111**:584-592 (Aug. 13) 1938. Spies, T. D.: Degenerative Diseases with Nutritional Interrelationships, South. M. J. **46**:238-247 (March) 1953. Nutrition and Disease, T. D. Spies, editor, Postgrad. Med. **17**:1-96 (March) 1955.

4. Mann, A. W.; Dreizen, S.; Pyle, S. I.; and Spies, T. D.: Red Graph and Wetzel Grid as Methods of Determining Symmetry of Status and Progress During Growth, J. Pediat. **32**: 137-150 (Feb.) 1948.

5. (*a*) Spies, T. D., and Stone, R. E.: Pituitary Adrenocorticotropic Hormone (ACTH) as Tool of Clinical and Laboratory Research, Lancet **1**:11-14 (Jan. 7) 1950. (*b*) Stone, R. E., and Spies, T. D.: Further Observations on Cortisone and ACTH as Therapeutic Agents, South M. J. **45**:885-896 (Oct.) 1952. (*c*) Spies, T. D.; Stone, R. E.; and Spies, H. A., Jr.: Metacortandracin and Delta 1 Dehydro-Hydrocortisone in Rheumatoid Arthritis, GP **12**:73-78 (July) 1955. (*d*) Spies, T. D., and others: Prednisone and Prednisolone as Therapeutic Agents: Progress Report on Their Integration into General Medical Practice, J. A. M. A. **159**:645-652 (Oct. 15) 1955.

6. (*a*) Spies, T. D.: Influence of Nutritional Processes on Aging, South. M. J. **50**:216-225 (Feb.) 1957. (*b*) Reference 5*d*.

7. Spies, T. D.; Aring, C. D.; Gelperin, J.; and Bean, W. B.: Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid, Am. J. M. Sc. **196**:461-475 (Oct.) 1938.

8. Himwich, H. E.; Spies, T. D.; Fazekas, J. F.; and Nesin, S.: Cerebral Carbohydrate Metabolism During Deficiency of Various Members of Vitamin B Complex, Am. J. M. Sc. **199**: 849-853 (June) 1940.

SYDENHAM'S CHOREA.—Data . . . suggest that Sydenham's chorea cannot be viewed simply as an organic disease caused by the various long-term consequences of the invasion of the child by bacteria. The evidence, totally considered, suggests rather that Sydenham's chorea is a much more complex disorder, and there is serious doubt that rheumatic fever plays a role in many patients with this illness. Other agents must be sought to explain this illness, and we feel that emotional and interpersonal factors are a promising avenue of such investigation.—A. H. Chapman, M.D.; Loraine Pilkey, M.A.; and M. J. Gibbons, M.S.S.W., A Psychosomatic Study of Eight Children with Sydenham's Chorea, *Pediatrics,* April, 1958.

ECHO-9 VIRUS EXANTHEMA

James T. Prince, B.S., Joseph W. St. Geme Jr., M.D.
and
William F. Scherer, M.D., Minneapolis

A morbilliform rash lasting from one to three days became epidemic in Minnesota in 1957. It occurred alone or in various combinations with fever and aseptic meningitis; the meningitis also occurred alone in six patients. Each strain of virus isolated from patients was identified by appropriate neutralization tests, and acute and convalescent phase human serums were assayed for neutralizing antibodies. The pathogen was thus found to be a strain of the enteric cytopathogenic human orphan virus ECHO-9. It resembled the prototype ECHO-9 in its behavior in cultures of cells from monkey kidney, human amnion, and the HeLa strain of human carcinoma, but it possessed the additional properties of pathogenicity for newborn mice and for tissue cultures of human foreskin cells. In its pathogenicity for newborn mice it resembled certain European, English, and Canadian strains of ECHO-9. This virus is believed to have caused as many as 400,000 infections in the whole state.

Exanthema caused by ECHO-9 virus, a recently recognized disease entity, must be differentiated clinically from other short-term exanthemas such as rubella, Boston exanthem,[1] and roseola infantum. Recognition of ECHO-9 virus in 1953 resulted from inoculation of monkey-kidney-cell cultures with material taken as a rectal swab from a healthy child in Ohio.[2] Known epidemics of ECHO-9-virus–induced aseptic meningitis occurred in Europe [3] and England [4] in 1955 and in 1956 and in Canada [5] in 1956. The epidemic syndrome was predominantly aseptic meningitis, although skin rash was seen in some patients.

During the summer of 1957 an epidemic of exanthema occurred in Minnesota. In summary of clinical details,[6] it can be stated that the patients presented a generalized morbilliform rash lasting one to three days. Some patients showed fever. Commonly, infection spread within families and within neighborhoods. While rash alone was common, symptoms of all patients made up a spectrum ranging from inapparent infection to skin rash with little disability, skin rash and fever, skin rash and aseptic meningitis, and, finally, aseptic meningitis without rash.

This article describes laboratory data establishing an etiological relationship between ECHO-9 virus and the epidemic exanthema seen in Minnesota during 1957. Two properties of the Minnesota strain of ECHO-9 virus are noteworthy: (*a*) pathogenicity for suckling mice in contrast to lack of such pathogenicity of the prototype ECHO-9 virus [2] and (*b*) pathogenicity for human foreskin cells in tissue culture.

(The incidence of disease from ECHO-9 virus in Minnesota during the summer of 1957 was estimated by the Minnesota Department of Health in a bulletin distributed to all physicians on Oct. 14, 1957. Instances of aseptic meningitis with or without exanthema were determined by canvass of 400 households randomly selected in the Minneapolis–St. Paul area. Projection from survey findings suggested that over 200,000 cases of ECHO-9 virus infection occurred during the summer of 1957 in the Minneapolis–St. Paul areas of Minnesota and that as many as 400,000 cases occurred in the whole state.)

From the Departments of Bacteriology and Immunology and of Pediatrics, University of Minnesota. Dr. Scherer is a John and Mary R. Markle Scholar in Medical Science.

Laboratory Methods

Specimens.—Stool specimens were frozen at –70 C in screw-capped glass jars within 12 to 24 hours after collection. Within a week, the feces were suspended to an approximate concentration of 20 Gm. per 100 ml. of glass-distilled water containing 0.001% phenol red. Supernatant fluid was harvested after centrifugation of specimens at 18,400 g for 30 minutes at 3 C; 200 units of penicillin and 100 mcg. of streptomycin (standard concentrations for this laboratory) were added per milliliter of fluid. These fluids, in sealed glass ampuls, were stored at –70 C for from days to weeks before inoculation into cell cultures or mice.

Throat swabs were immersed in 3 to 4 ml. of nutrient broth immediately after collection. Thereafter, the broth was centrifuged and stored as described above. Serum specimens representative of acute and convalescent phases of disease were stored at –20 C.

Preparation of Cell Cultures.—Primary cell cultures of cynomolgus and rhesus monkey kidney and of human amnion and cultures of HeLa cells were prepared as described.[7] For virus isolation or neu-

tralization tests, monkey kidney cells in 16-by-125-mm. tubes were maintained under 0.8 ml. of Hanks' balanced salt solution (BSS) containing 2% calf serum, 0.5% lactalbumin hydrolysate, and antibiotics. Similar cultures of HeLa and human amnion cells were washed thrice with one milliliter of BSS and maintained under 0.8 ml. of BSS containing 10% calf serum, 0.1% Difco Yeastolate, and antibiotics.

Human foreskin tissue was cut with scalpels into pieces approximately 1 mm. in diameter, embedded on coverslips in chicken plasma clotted with chicken embryonic extract, placed in Leighton tubes, and incubated in BSS containing 10% human serum, 0.1% yeast extract, and antibiotics. When at least one explant per culture developed a corona of fibroblast-like cells, each selected culture was rinsed twice with 2 to 3 ml. of BSS and covered with 0.8 ml. BSS containing 10% calf serum, 0.1% yeast extract, and antibiotics. All cultures were grown or maintained for virus tests at 37 C.

Isolation of Virus.—Tube cultures of monkey kidney, HeLa, or human amnion cells were inoculated with 0.1 ml. of undiluted virus specimen and incubated at 37 C. Cells magnified 50 or 100 times were observed for 10 days or, in the case of foreskin cultures, for 21 days. Newborn Swiss albino mice (from litters no older than 48 hours) were concomitantly inoculated intracerebrally with 0.02 ml. and intraperitoneally with 0.05 ml. of virus specimen and observed for 14 days.

Identification of Virus.—Each ECHO-9 virus strain isolated from patients was identified by neutralization test with monkey-kidney-cell cultures. Test virus (75-250 $TCID_{50}$) was incubated with homotypic monkey antiserum containing 20 units of ECHO-9 neutralizing antibody, according to the technique recommended by the committee on ECHO Viruses.* Cultures incubated at 37 C were observed for five days. Virus-neutralization tests done with human foreskin cultures or mice as indicators were performed similarly, except that cultures were observed for 21 days and mice for 14 days. Neutralization tests for ECHO-9 virus as 10% mouse-muscle suspensions involved use of 50 units of antibody and concomitant intracerebral inoculation of 0.02 ml. and intraperitoneal inoculation of 0.05 ml. of antibody-virus mixture.

Assay for ECHO-9 Neutralizing Antibody in Serum.—Neutralizing antibodies were titrated with primary monkey-kidney-cell cultures. Test human serums were serially diluted twofold in the maintenance medium specified for kidney cells. Serum dilutions were mixed 1:1 with virus suspension representing 150-500 $TCID_{50}$ per milliliter; mixtures were incubated for one hour at room temperature (22-30 C). Each virus-serum mixture in 1-ml. amount was inoculated into two tube cultures containing only cells attached to glass (no fluid medium). Cultures were incubated at 37 C and observed under the microscope on day 1 or 2 and day 5. Titration end-points represented the highest

TABLE 1.—*Evidence for ECHO-9 Virus Infection in Patients with Exanthem and/or Aseptic Meningitis*

Syndrome Class	Patient No.	Age, Yr.	Sex	Onset of Symptoms, Date	Virus Isolated (+) or (0) from: Throat Swabs	Stools	Spinal Fluid	Homotypic Neutralizing Antibody Titer: Acute Phase Serum	Convalescent Phase Serum
Exanthem only	1A*	2.5	M	7/20	+(3)† ...	... ...		<10(3)‡	80(31)
	2	23	F	7/21	+(4) ...	... ...		<10(4)	80(23)
	3	7	M	7/21	+(7) ...	+(11) 0(9)		<10(7)	40(39)
	4A	6	M	7/22	+(1) ...	+(10) ...		<10(3)	80(31)
	5B	2.5	M	7/25	+(4,10) 0(29)	... ...		<10(4)	80(28)
	6C	33	M	7/27	+(4) ...	... ...		<10(4)	40(18)
	7C	35	F	7/27	+(5) ...	... ...		<10(4)	80(24)
	8B	4	M	7/31	+(4) 0(23)	+(6) ...		4(4)	>128(22)
	9	10	F	8/17	+(3) 0(4)	+(8) 0(13)		<10(3)	40(33)
	10	3	F	8/18	... 0(2)	+(3) ...		<10(2)	80(32)
					10/14§ ...	5/7§ ...		...	...
Exanthem and aseptic meningitis	11	7	F	7/28	... ...	+(9) 0(7,8)		<10(7)	80(43)
	12	13	M	7/28	... ...	+(9) 0(7,8)		<10(7)	10(18)
	13	14	F	8/ 3	+(6) ...	+(7,11) ...		<10(6)	160(34)
	14	9	M	8/ 9	... ...	+(2,4,5) ...		<10(3)	80(33)
	15	7	M	8/28	... ...	... ...		<10(3)	40(34)
					1/1§ ...	7/11§ ...		...	...
Aseptic meningitis	16	11	M	7/17	... ...	+(9,6) ...	+(4)	<10(6)	160(56)
	17A	26	F	7/23	... ...	... ...		<10(8)	>640(30)
	18	38	M	7/30	... ...	+(5) ...	+(3)	<10(3)	40(45)
	19B	29	F	7/31	... ...	... ...		<10(<795)	80(31)
	20	3.5	M	7/31	... ...	... ...		<10(6)	>320(42)
	21	9	F	9/ 3	... ...	... 0(1)		<10(1)	40(48)
					... ...	3/4§ ...	2/2§	...	...
Fraction of all specimens positive					11/15 (0.73)	15/22 (0.68)	2/2 (1.00)	21/21 (1.00)	

* A, etc., designates patients from single families.
† Figure in parenthesis is day of illness when specimen was obtained, counting the first day of symptoms as day 1.
‡ Neutralizing antibody titers are given as highest dilution of serum that completely neutralized 75 to 250 $TCID_{50}$ of ECHO-9 virus from patient 6 when tested in two tube cultures of monkey kidney cells.
§ Fraction of specimens positive.

serum dilution completely preventing cell destruction in both cultures. Antibody assays were accompanied by control titrations of test virus to determine exact virus dosage as $TCID_{50}$. For this purpose, virus was mixed 1:1 with calf-serum medium.

Results

At the beginning of the exanthema epidemic in Minnesota during the summer of 1957, the disease was thought possibly to be Boston exanthem,[1] now classified as infection by ECHO-16 virus or a closely related agent.[9] The Boston exanthem virus was described originally as cytopathogenic for fibroblasts but not epithelial cells.[1] In initiating study of the Minnesota epidemic, tissue cultures of human fibroblasts were therefore used in attempts to recover an etiological agent. Additional inoculation of material from throat swabs and feces into monkey-kidney-cell cultures, however, resulted in prompt recovery of ECHO-9 virus. Because it was then evident that the exanthema involved ECHO-9 virus rather than the agent of Boston exanthem, monkey-kidney-cell cultures were used for the remaining virus isolation tests.

Correlation of Exanthema with Human ECHO-9 Virus Infection.—Fifteen exanthematous patients (table 1) yielded complete series of specimens, including acute and convalescent-phase serums, throat swabs, and/or feces. These patients ranged in age from 2.5 to 35 years; their illnesses began between July 20 and Aug. 28, 1957. Fifteen throat swabs were obtained from 11 patients; 11 swabs from 10 patients yielded ECHO-9 virus upon inoculation into monkey-kidney cultures (table 1). Although most throat swabs yielding virus were taken between the 1st and 5th days of illness, virus was isolated from a swab taken as late as the 10th day of illness. Eighteen fecal specimens were obtained from 9 patients; 12 specimens, representing each of the 9 patients, yielded ECHO-9 virus (table 1). Tests for homotypic ECHO-9 neutralizing antibody were done on serum obtained on days 2 to 7 of illness (acute phase) or days 18 to 39 (convalescent phase). A fourfold or greater increase in antibody titer was found for each of the 15 patients (table 1).

Evidence that ECHO-9 virus did not cause all cases of exanthema occurring in Minnesota during July and August, 1957, is summarized in table 2.

TABLE 2.—*Instances of Undiagnosed Exanthem Concurrent with ECHO-9 Epidemic of July-August, 1957*

Syndrome Class	Patient No.	Age, Yr.	Sex	Onset of Symptoms, Date	Virus Not Isolated (0)* from Throat Swab	Virus Not Isolated (0)* from Stool	Homotypic Neutralizing Antibody Titer: Acute Phase Serum	Homotypic Neutralizing Antibody Titer: Convalescent Phase Serum
Exanthem	22	5	M	7/21	0(9)†	0(8)	10(7)‡	<4(31)
	23	2	F	7/28		0(3)	<4(2)	<4(31)
	24	1	F	7/31	0(5)	0(5)	<4(4)	<4(24)
	25	2	M	8/1	0(1)	0(2)	<4(1)	<4(31)

* Specimens were tested in monkey kidney cells, Hela cells, human amnion cells, foreskin fibroblast explant cultures, and litters of 1-to-2-day-old mice inoculated intraperitoneally and intracerebrally.
† Figure in parenthesis is day of illness when specimen was obtained, counting the first day of symptoms as day 1.
‡ Neutralizing antibody titers are given as highest dilution of serum that completely neutralized 75 to 250 TCD50 of ECHO-9 virus from patient no. 6 (table 1) when tested in cultures of monkey kidney cells. These results were confirmed by repeated tests.

TABLE 3.—*Pathogenicity of ECHO-9 Viruses for Cultivated Foreskin Fibroblasts and for Newborn Mice; Comparison of Viruses in Patients' Specimens with Viruses Passed Once in Monkey-Kidney Culture*

Patient, No.	Syndrome	ECHO-9 Virus Isolated from	Fraction of Indicator Hosts Exhibiting Pathogenic Effect: Foreskin Fibroblasts (Cytopathogenicity): Specimen	Foreskin Fibroblasts (Cytopathogenicity): First Passage	1-to-2-Day-Old Mice Injected Intracerebrally and Intraperitoneally (Paralysis): Specimen	1-to-2-Day-Old Mice Injected Intracerebrally and Intraperitoneally (Paralysis): First Passage
2	Exanthem	Throat swab (4)*	0/3†	3/3‡	0/8 0/8†	0/9 0/10
3	Exanthem	Throat swab (7)	1/3§	3/3	0/9 0/11	8/9 5/7§
		Stool (11)	0/3	3/3	0/7 0/7	0/6 2/13
4	Exanthem	Throat swab (1)	0/3	3/3	0/8 0/8	0/5 0/7
5	Exanthem	Throat swab (4)	0/3	3/3	0/5 0/8	0/8 2/12
6	Exanthem	Throat swab (4)	2/3	3/3	0/10 0/8	6/6 7/7
9	Exanthem	Throat swab (3)	0/3	3/3	0/7 0/7	8/8 6/6
		Stool (8)	0/3	3/3	0/6 0/6	2/10 3/7
10	Exanthem	Stool (3)	0/3	3/3	0/10 0/7	1/9 4/6
11	Exanthem & Aseptic Meningitis	Stool (3)	0/3	3/3	0/10 0/7	2/10 3/7
16	Aseptic Meningitis	Spinal fluid (2)	2/3	3/3	5/12 0/7	6/9
19	Aseptic Meningitis	Stool (4)	0/3	3/3	0/12 0/10	0/5 0/6
		Spinal fluid (2)	0/3	3/3	0/8 0/7	0/6 7/8
Fraction of specimens pathogenic			3/13 (0.23)	13/13 (1.00)	1/13 (0.08)	10/13 (0.77)
Fraction of virus strains pathogenic			3/10 (0.30)	10/10 (1.00)	1/10 (0.10)	8/10 (0.80)

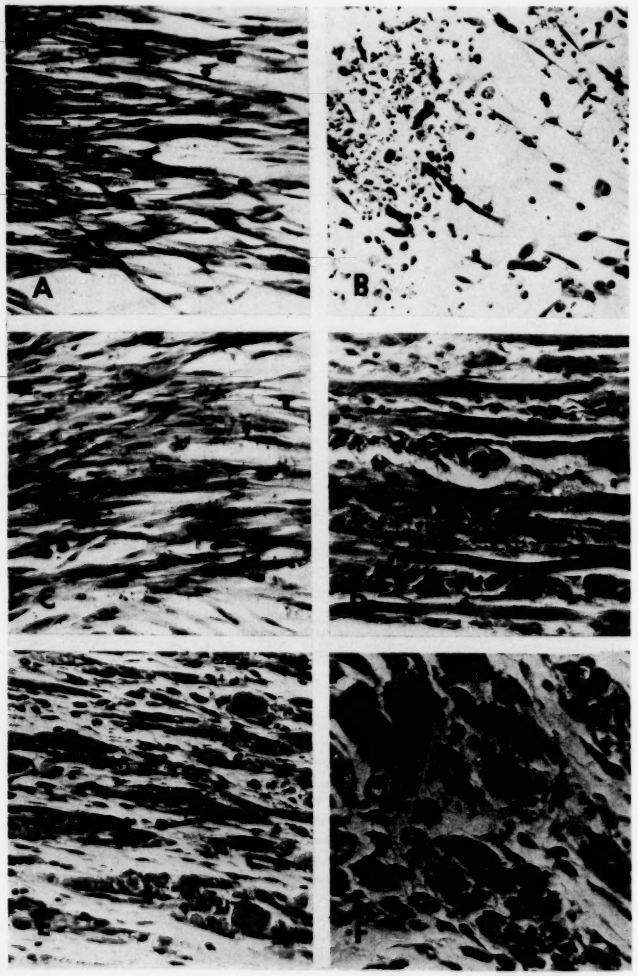
* Figure in parenthesis is day of illness when specimen was obtained, counting the first day of symptoms as day 1.
† Numerator signifies the number of fibroblast cultures that showed cell destruction, or number of mice paralyzed. The denominator indicates the number of cultures inoculated or number of mice per litter. For mice, each fraction represents one litter. Positive results are shown in bold-face type.
‡ Each virus from first-passage fibroblast cultures inoculated with ECHO-9 strains that were originally isolated in monkey-kidney cultures was neutralized by ECHO-9 monkey antiserum upon second passage in fibroblasts and in monkey-kidney cells.
§ Each virus from first-passage fibroblast cultures inoculated with specimens from patients 3, 6, and 16 was neutralized by ECHO-9 monkey antiserum upon second passage in fibroblasts and in monkey-kidney cells.
‖ Each virus from first-passage mice (as suspensions of hind limb muscle) was neutralized by ECHO-9 monkey antiserum in 1-to-2-day-old mice (inoculated IC and IP) and in monkey-kidney-cell cultures.

Four patients, from 1 to 5 years of age, developed skin rash between July 21 and Aug. 1. However, ECHO-9 virus was not recovered from throat swabs or stool specimens, and neutralizing serum antibodies did not appear in significant concentration or increasing titer. Specimens were examined for virus by inoculation of monkey kidney, human foreskin, human amnion, and HeLa cultures and of newborn mice. The fact that the clinical manifestations of disease in these four patients were indistinguishable from illnesses established for other patients as ECHO-9 virus infection emphasizes need for laboratory confirmation of clinical diagnoses of ECHO-9 virus exanthema and/or aseptic meningitis.

Correlation of Aseptic Meningitis with Human ECHO-9 Virus Infection.—Five of the 15 patients with exanthema suffered aseptic meningitis; 6 other

patients exhibited evidence only of aseptic meningitis (table 1). Serum neutralizing antibody titers for all patients rose during convalescence, and ECHO-9 virus was recovered from feces and/or throat swabs. Cerebrospinal fluid obtained from two patients (16 and 19, table 1) on the fourth and third respective day of illness yielded ECHO-9 virus. This laboratory evidence supported the conclusion that ECHO-9 virus has caused aseptic meningitis in these patients.

Family Infections by ECHO-9 Virus.—Three families were studied. In table 1, patients 1, 4, and 17 represent family A; patients 5, 8, and 19 represent family B; and patients 6 and 7 represent family C. In these families, onset of illness occurred sequentially over a period of several days (table 1); apparently, ECHO-9 virus had either spread rapidly in the families or simultaneously infected several family members who varied in period of incubation. ECHO-9 virus was recovered from two other sick members of family A, children aged 1 and 3, from throat swabs obtained on the third days of illness. A fourth member of family B, a child aged 1, yielded ECHO-9 virus from feces obtained on the fifth day of his illness. However, the fifth member of family B, the father, showed no evidence of infection by ECHO-9 virus by test of serum obtained (*a*) prior to the epidemic and (*b*) about 35 days after onset of disease in other family members. These findings suggested that family infections were common but that it was possible for a family member to escape infection.



A, *B*, and *C*, foreskin fibroblasts stained with hematoxylin and phloxin (magnification 100×). *A*, normal fibroblasts. *B*, remnants of fibroblasts destroyed six days after inoculation of ECHO-9 virus as first-passage monkey-kidney harvest from the throat swab patient of 6 (table 1). *C*, normal fibroblasts in a culture seven days after inoculation of the same virus as in *B* and ECHO-9 monkey antiserum. *D* and *E* (magnification 200 ×) and *F* (magnification 400 ×), infant mouse muscle stained with hematoxylin and eosin. Mice were inoculated with first-passage monkey-kidney harvests of ECHO-9 virus from, *D*, patient 6 and, *E*, and *F*, patient 3. Note necrosis of myofibrils, inflammatory cells, and disruption of normal muscle morphology.

Pathogenicity of Minnesota Strain ECHO-9 Virus for Foreskin Cells and for Newborn Mice.—The initial use of human foreskin cell cultures to detect Boston exanthem agent revealed an interesting biological behavior of the ECHO-9 virus responsible for epidemic exanthema in Minnesota during July and August, 1957. Foreskin cultures containing predominantly fibroblasts were inoculated with material from six throat swabs, five stool specimens, and two cerebrospinal fluids obtained from a group of 10 patients made up of 7 with exanthema, 1 with exanthema and aseptic meningitis, and 2 with only aseptic meningitis (table 3). These 13 specimens had yielded 10 strains of ECHO-9 virus upon inoculation into monkey kidney cultures. Yet only 3 of the 10 virus strains (from patients 3, 6, and 16, table 3) caused destruction of foreskin cells. The three viruses isolated in foreskin cultures were identified by neutralization test with ECHO-9 monkey antiserum upon passage in monkey-kidney cultures and again in human foreskin cultures.

After primary passage of the 10 strains of ECHO-9 virus in monkey-kidney cultures, they behaved differently in foreskin cultures. Whereas only 3 original specimens from patients destroyed foreskin fibroblasts, each of the 10 virus strains after passage in monkey-kidney cells produced such destruction (table 3). Parts *A*, *B*, and *C*, in the figure show representative cytologic effects of ECHO-9 virus strains on foreskin fibroblasts and prevention by ECHO-9 antiserum.

While the prototype of ECHO-9 virus is not pathogenic for newborn mice, certain ECHO-9 strains isolated in England,[4b] Europe,[3] and Canada [5] cause paralysis and death of newborn mice. Ten virus strains isolated in Minnesota during 1957 were therefore inoculated both intracerebrally and intraperitoneally into 1-to-2-day-old mice; these strains were the same as those inoculated into foreskin cultures (table 3). One group of test mice from two litters was inoculated with corresponding virus harvested from monkey-kidney cultures. Only one original specimen, cerebrospinal fluid from patient 16, produced disease in newborn mice (table 3). In contrast, 8 of 10 virus strains harvested after primary passage in monkey-kidney cultures affected newborn mice; infection was revealed by extensor paralysis of hind limbs, which characteristically did not culminate in death but gradually became milder, with eventual recovery of the mouse. Histopathology of this acute myositis of mice is shown in parts *D*, *E*, and *F* in the figure. The pathogenicity for mice and monkey-kidney cells of muscle suspensions prepared from sick mice was neutralized by ECHO-9 monkey antiserum.

Comment

The results of these studies established that ECHO-9 virus was the etiological agent of an epidemic of exanthema in Minnesota during summer of 1957. The ECHO-9 disease ranged from mild exanthema to mixtures of exanthema and aseptic meningitis and to moderately severe but nonfatal aseptic meningitis; however in the patients studied, the skin rash predominated. Epidemiologic findings suggested that the disease had been highly communicable, especially in families.

This establishment of an etiological relationship between ECHO-9 virus and exanthema should not lead clinicians to the general conclusion that all summer rashes are caused by ECHO-9 virus. Such a conclusion would not be valid even were an epidemic of ECHO-9 virus-induced disease existent in a community. Evidence against such a conclusion is presented by findings for the four patients (table 2) who suffered skin rash indistinguishable from that caused by ECHO-9 virus but failed to yield laboratory evidence of ECHO-9 virus infection. These patients likewise did not show evidence, in the form of antibody response, of infection by ECHO-16 virus (either identical or closely related to Boston exanthem agent), ECHO-2 or 14 viruses, or Coxsackie A9, B2, or B5 viruses. The last virus was responsible for sporadic cases of aseptic meningitis in 1957 concurrent with epidemic ECHO-9 virus disease and for epidemic aseptic meningitis in 1956.[10]

In comparison with the prototype of ECHO-9 virus, recovered in 1953 from a healthy child in Ohio,[3] Minnesota strains were distinctive in their pathogenicity for newborn mice. In this respect, the Minnesota strains resembled strains recovered in Europe, England, and Canada during 1955 and 1956. The property of mouse pathogenicity of ECHO-9 virus strains is important in consideration of whether the virus should be classified as Coxsackie or ECHO. Further discussion of this point is not relevant to this paper; a recent analysis of the problem may be consulted for additional information.[11]

The striking change in capacity of Minnesota ECHO-9 viruses to produce disease in mice or destroy foreskin fibroblasts in culture apparently conditioned by passage of the viruses in primary monkey-kidney cultures is noteworthy but unexplained. A single passage in monkey-kidney-cell cultures could have produced such change by (*a*) increasing the concentration of virus and/or (*b*) inducing or permitting qualitative change in virus properties; either quantitative or qualitative changes in virus could result in increased pathogenicity for mice and foreskin fibroblasts.

Summary

ECHO-9 virus was identified by tests with cell cultures and infant mice as the etiological agent of an epidemic of exanthema occurring in Minnesota during the summer of 1957. Infection was manifest by a spectrum including morbilliform rash (most common) and/or aseptic meningitis. Minnesota

ECHO-9 strains were cytopathogenic for monkey-kidney epithelium and human foreskin fibroblasts; they differed from the prototype of ECHO-9 virus and resembled European, English, and Canadian strains in their pathogenicity for newborn mice.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc., New York, and by contract with the Communicable Disease Center, U. S. Public Health Service.

References

1. Neva, F. A., and Enders, J. F.: Cytopathogenic Agents Isolated from Patients During Unusual Epidemic Exanthema, J. Immunol. **72:**307-314 (April) 1954

2. Ramos-Alverez, M., and Sabin, A. B.: Characteristics of Poliomyelitis and Other Enteric Viruses Recovered in Tissue Culture from Healthy American Children, Proc. Soc. Exper. Biol. & Med. **87:**655-661 (Dec.) 1954.

3. Nihoul, E.; Quersin-Thiry, L.; and Weynants, A.: ECHO Virus Type 9 as Agent Responsible for Important Outbreak of Aseptic Meningitis in Belgium, Am. J. Hyg. **66:**102-118 (July) 1957.

4. (*a*) Boissard, G. P. B.; Stokes, L. J.; Macrae, A. D.; and MacCallum, F. O.: Isolation of Viruses Related to ECHO Virus Type 9 from Outbreaks of Aseptic Meningitis, Lancet **1:**500 (March) 1957. (*b*) McLean, D. M., and Melnick, J. L.: Association of Mouse Pathogenic Strain of ECHO Virus Type 9 with Aseptic Meningitis, Proc. Soc. Exper. Biol. & Med. **94:**656-660 (April) 1957.

5. Laforest, R. A., and others: Outbreak of Aseptic Meningitis (Meningoencephalitis) with Rubelliform Rash: Toronto, 1956, Canad. M. A. J. **77:**1-4 (July) 1957.

6. St. Geme, J. W.: Unpublished data.

7. Melnick, J. L.: Application of Tissue Culture Methods to Epidemiological Studies of Poliomyelitis, Am. J. Pub. Health **44:**571-580 (May) 1954. Syverton, J. T.; Scherer, W. F.; and Ellwood, P. M.: Studies on Propagation in vitro of Poliomyelitis Viruses: V. Application of Strain HeLa Human Epithelial Cells for Isolation and Typing, J. Lab. & Clin. Med. **43:**286-302 (February) 1954. Syverton, J. T., and Scherer, W. F.: Application of Mammalian Cells in Continuous Culture for Assays in Virology, Ann. New York Acad. Sc. **58:**1056-1071 (Nov. 17) 1954. Takemoto, K. K., and Lerner, A. M.: Human Amnion Cell Cultures: Susceptibility to Viruses and Use in Primary Virus Isolation, Proc. Soc. Exp. Biol. & Med. **94:**179-182 (Jan.) 1957.

8. Committee on ECHO Viruses: Enteric Cytopathogenic Human Orphan (ECHO) Viruses, Science **122:**1187-1188 (Dec. 16) 1955.

9. Neva, F. A.: Personal communication.

10. Syverton. J. T., and others: Outbreak of Aseptic Meningitis caused by Coxsackie B5 virus, J. A. M. A. **164:**2015-2019 (Aug. 31) 1957.

11. Committee on Enteroviruses, National Foundation for Infantile Paralysis: Enteroviruses, Am. J. Pub. Health **47:**1556-1566 (Dec.) 1957.

TREATMENT OF PULMONARY INSUFFICIENCY BY TRACHEAL FENESTRATION

PRELIMINARY REPORT

Edgar Mayer, M.D., Charles F. Blazsik, M.D.
and
Israel Rappaport, M.D., New York

Tracheal fenestration is an operation to provide a permanent access to the deeper airways. The stoma can be kept open or closed at will. Its use is here proposed as a new method of treatment in advanced pulmonary insufficiency. The four patients whose cases are described were approaching terminal hypoxia as a result of destructive pulmonary disease. Tracheal fenestration made it possible to remove mucopulmonary secretions by aspiration. The patient gradually learns to do this himself. The immediate relief experienced by the patient after aspiration, and the striking change for the better in the course of the disease in these four cases, indicate that the advantages of tracheal fenestration need to be explored further.

In the treatment of patients with pulmonary insufficiency efforts are now directed toward the relief of hypoventilation by means of mechanical ventilators. Since practical experience has shown that mechanical aids to ventilation are operated most efficiently when used in connection with intratracheal tubes, tracheostomy is being increasingly resorted to in "hypoventilation crises."[1] Such tracheostomies are now usually performed as emergency measures and chiefly as adjuncts to the use of mechanical ventilators.

Current procedures, we believe, fall far short of the real goal of treatment of pulmonary insufficiency, and we are accordingly proposing tracheal fenestration as a new method of treatment. When performed at an early phase of pulmonary insufficiency, we have found that it provides an excellent means both of maintaining the airways free of obstructing secretions and of keeping them well ventilated. Elective tracheal fenestration not only

obviates the need for mechanical ventilation but also makes possible the prevention of "hypoventilation crises." Such prevention, we feel, should be the goal of treatment in pulmonary insufficiency, the clinical course of which is characterized by a sequence of such crises, which may lead to death by apnea and asphyxia.

In this preliminary report we wish to discuss the following three aspects of this new method of treatment: (1) the need for early and permanent tracheal opening in pulmonary insufficiency, (2) possible accomplishment by elective tracheal fenestration, and (3) mode of action.

Advantage of Preexisting Tracheal Opening

The need for early and permanent tracheal opening in pulmonary insufficiency was impressed upon us through certain clinical observations in patients whose lives were greatly prolonged and made comfortable by means of a preexisting tracheal opening which had been used to great advantage in maintaining open and well-ventilated airways. The following case history will best demonstrate this.

Case 1.—A frail middle-aged woman had extensive confluent tuberculosis involving both her lungs and her larynx. The tuberculosis of the larynx threatened airway obstruction, and the patient required a tracheotomy with cannula at an early phase of the disease. The process resulted in complete destruction of her left lung, with vast honeycombing of giant cavities producing large quantities of pus. In the right lung the disease progressed at a slower rate. She lived to benefit from chemotherapy, which arrested the lesions in the right lung, leaving it in a state of advanced fibrosis and emphysema. Eventually she was left with a pulmonary reserve so low that it barely permitted her more than a bedridden life. The chest x-ray (fig. 1) demonstrates her pulmonary disease at that time.

We observed this invalid patient for 10 years, during which her life depended almost entirely on the skillful maintenance of patent and ventilated airways attained through frequent bronchial intubation and aspiration with the aid of a small bedside suction pump. At first large amounts of secretions, accumulated in the giant cavities of her left lung, had to be eliminated through the tracheostomy cannula. Asphyxia became a constant threat until finally she dared to discard the cannula. This enabled her to rapidly pass a wider catheter through the naked tracheal stoma. Employing a "to and fro" motion and through the use of stronger suction she was enabled to get rid of much viscid mucopus adhering to both the airways and the tubes. Through these manipulations the airways were kept clear most of the day, eventually requiring fewer and fewer "treatments." As her pulmonary reserve diminished and as the secretions became scant she practiced frequent intubations with a few rapid aspirations. These, she explained, relieved her of a feeling of "tightness in the chest," a symptom usually followed by periods of shortness of breath. It became apparent to us that these intubations and aspirations afforded ventilation and probably relieved air trapping in the lung. At this stage the secretions aspirated had changed in character to very scant colorless, sticky, stringy mucus. During this long protracted period of precarious existence this patient had survived several attacks of biliary colic as well as an operation for the removal of a breast cancer carried out while she was under local anesthesia. She died eventually of "intestinal obstruction from metastatic carcinoma."

Case 2.—A male, aged 47, gave a history of chronic pulmonary tuberculosis of 10 years' duration resulting in extensive fibrosis in both upper lobes, more extensive on the right. With a recent flare-up, severe laryngeal tuberculosis developed, threatening airway obstruction, which required tracheostomy with a cannula. Simultaneously there developed widespread extension of tuberculosis throughout both lungs. Although chemotherapy resulted in much clearing of the recent lesions, there remained so much fibrosis and emphysema that the patient's pulmonary reserve became greatly reduced by the time his tuberculosis healed. Due to this fibrosis and emphysema there was persistent dyspnea, aggravated by continued cough and expectoration characteristic of patients with emphysema and bronchiolitis of any origin. The secretions, although moderate in quantity, were very viscid and difficult to raise through the tracheal cannula. Much relief was now obtained by intubation, aspiration, and inhalation of bronchodilators.

This patient, like the one previously described, was soon led to discard the tracheostomy cannula and to practice intubation and aspiration through the naked stoma in the trachea. Here likewise the material aspirated changed to

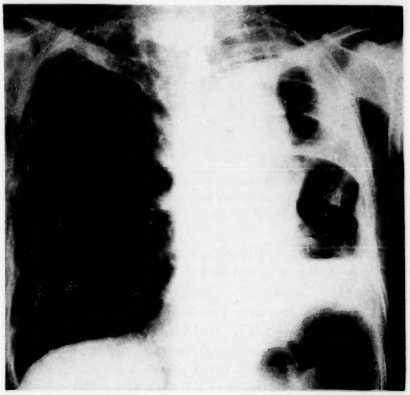


Fig. 1.—Chest roentgenogram of patient in case 1, showing severe pulmonary disease.

scant, stringy, sticky mucus. This patient also resorted to aspiration of air from his lungs when he felt tightness in the chest, which was usually the premonitor of attacks of dyspnea. These attacks he could prevent by a few rapid aspirations, which he was then able to follow with vigorous inspirations. He practiced this regularly after exertions as well as after long periods of sleep in anticipation of dyspneic attacks which were signaled by the chest tightness. He acquired the habit of testing his breathing for the need of aspiration by periodic hyperventilation exercises, and for a time it appeared that he might become a habitual hyperventilator. Eventually he learned to manage without aspiration for weeks and then months and resorted to it only for short periods during intercurrent respiratory infections occurring about three to four times yearly. These bronchitic periods were cut short by preventing the accumulation of secretions and the aggravation of his emphysema from protracted cough. Observing this patient over a 10-year period convinced us that the benefits derived from the use of his tracheal opening allowed this patient to live in relative comfort

despite severe emphysema, extensive pulmonary fibrosis, and marked reduction of pulmonary reserve, as indicated in the x-ray (fig. 2).

In both patients we observed that the creation of a tracheal opening at an early phase of the disease enabled them to prolong their lives greatly

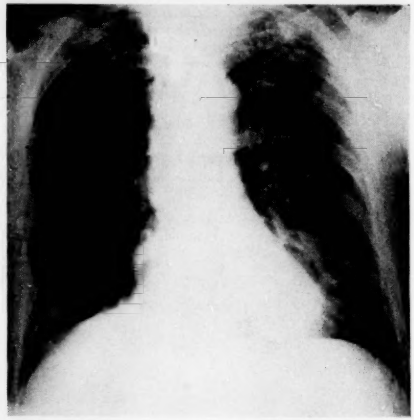


Fig. 2.—Chest roentgenogram of patient in case 2, showing severe emphysema, extensive pulmonary fibrosis, and marked reduction of pulmonary reserve.

despite their low pulmonary reserve. We were able to draw certain significant conclusions: As the pulmonary capacity progressively diminished, these patients became increasingly sensitive to the least interference with ventilation and less tolerant of secretions accumulated in their airways. They increasingly practiced intubation and aspiration to maintain the airways free of secretions. Eventually they aspirated the airways even when little secretion was present. This could serve as a means of creating air currents in their lungs for purposes of ventilation. The early presence of the tracheal opening, enabling these patients to keep their airways clear, has, we believe, prevented added secondary infections, forestalled greater loss of pulmonary capacity, and prevented progression of the emphysema and bronchiolitis in the opposite lung as well as progression to hypoventilation crises so characteristic of advancing pulmonary insufficiency. In view of the irreversible character of the latter, the need for a permanent tracheal opening appears to us obvious. In short, our observations led us to believe that an early as well as a permanent tracheal opening should be a useful means of prolonging the lives of patients with low pulmonary reserve. Accordingly, we began treating such patients by the creation of a permanent tracheal opening.

Clinical Trials of Tracheal Fenestration

The surgical procedure for creating a permanent window in the trachea which can be kept open or closed at will was worked out by Dr. E. E. Rockey after extensive animal experimentation. This procedure was described by us in recent joint publications.[2] Suffice it to point out here that this also involves a preliminary tracheostomy with cannula through which inhalation and aspiration is practiced for the first few weeks until the tracheal fenestration above it heals and becomes available for permanent use. Two reports follow of patients treated with such fenestration. The operations were performed by Dr. Rockey, who also supervised the subsequent treatment with specially designed bronchial catheters, enabling intubation and aspiration in either side of the chest.

Case 3.—A 52-year-old man gave a history of chronic bronchitis since childhood. However, this condition did not prevent him from playing football for many years, into his late 30's. He dates his illness to postoperative pulmonary complications suffered in 1948, when he was operated on for a double hernia. From that time on, he had suffered from almost constant shortness of breath but with little cough and only scant expectoration. A diagnosis of asthma was given, and he was repeatedly treated accordingly with injections of such drugs as epinephrine. In May, 1956, spontaneous pneumothorax brought him into the hospital in serious condition. He was hospitalized for several weeks. A recurrence of pneumothorax in July, 1956, again confined him to the hospital for several weeks. In August, 1956, he was rehospitalized in a critical condition, and he has remained in the hospital to

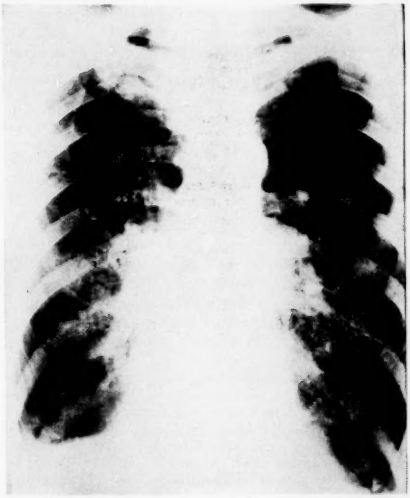


Fig. 3.—Chest roentgenogram of patient in case 3, showing pneumothorax.

the time of writing. The chest x-rays (fig. 3) show the characteristic picture of vanishing lungs with a pneumothorax on the left.

For the first two months in the hospital the patient spent much time in an oxygen tent until his lung reexpanded. After that he continued to suffer from extreme dyspnea. In 1957 he was treated for several severe attacks of aggravated dyspnea but with no pneumothorax. He was treated with steroids, with only temporary response, but with the aid of bronchodilators and oxygen inhalation he was able to continue a precarious existence, barely managing the few steps from bed to bathroom. His exercise tolerance was practically zero, and he was steadily growing weaker and approaching terminal hypoventilation. This was his condition in October, 1957, when he submitted to tracheal fenestration as a last resort. Almost immediately after aspiration of an unexpectedly large amount of mucopurulent secretion his dyspnea was greatly relieved. Five days later he could walk 20 yd. with little shortness of breath, and one week later he could walk twice that distance back and forth. Three weeks after operation he was up and about most of the day and could even ascend a flight of 12 stairs without dyspnea. At first he required frequent aspirations (8 to 10 times daily) and eliminated large amounts of mucopurulent secretions. After a few weeks the amount of secretion diminished greatly (to 4 to 5 cc.), and he required aspiration only three times daily. The patient stated, "I feel like a different man." He slept through the nights without need of aspiration. Three months after operation, he was able to intubate himself with ease whenever he felt the need. By then he was up and about, leading an almost normal life. He now feels fit to resume his previous work.

CASE 4.—A 63-year-old man had been suffering from chronic pulmonary tuberculosis since 1950. He had extensive disease involving both lungs, for which he was hospitalized for a period of over two years, from early 1954 until the latter part of 1956. By then much healing of the tuberculous lesions occurred, with extensive fibrosis in both upper lobes, but the sputum was still positive by culture as late as July, 1957. However, with progressive healing of the lesions in his lungs he became increasingly disabled by shortness of breath. In April, 1957, he reentered the hospital chiefly because of persistent dyspnea. The chest x-ray (fig. 4) illustrates the extent of fibrosis and emphysema, which amply accounts for his pulmonary insufficiency at that time. This was greatly aggravated by a severe bronchitis which was present, constantly causing cough with expectoration of about 60 cc. daily. Physical signs corroborated the severe emphysema in both lungs.

Throughout 1957 the patient's general condition deteriorated steadily and he remained hospitalized as a pulmonary cripple, became increasingly bedridden, and required oxygen often for short periods throughout the day. By December, 1957, he could no longer walk the short distance from his bed to the bathroom without experiencing exhausting dyspnea. As a last resort tracheal fenestration was performed in December, and large amounts of mucopus were aspirated both during and after the operation. Almost immediately the urgent dyspnea abated, and he no longer required oxygen. At first the amount of aspirated purulent secretions increased, but soon they decreased and changed to viscid mucus. The breathing improved so remarkably that two weeks after operation he could walk freely about the hospital corridor and even denied dyspnea on mild effort. On Jan. 1, 1958, when the tracheal cannula was removed, he was free of apparent dyspnea, and since then he has been a semiambulant patient. He continues to intubate and aspirate himself about four times daily. He is now fit for light work.

Although in both patients tracheal fenestration was performed recently, we feel justified in presenting this preliminary report, because the immediate results have been so strikingly favorable. We are convinced that these patients will continue to enjoy the benefits from fenestration as did those who were under our observation for many years with their permanent tracheostomy. These results are all the more remarkable since we were not dealing with truly early stages of pulmonary insufficiency. In fact, both patients were practically in critical condition when operated on. In both cases severely disabling and distressing dyspnea was relieved soon after institution of a tracheal opening when efficient intubation and aspiration through the tracheostomy cannula was possible. By the time the fenestration had healed sufficiently for the patients themselves to begin passing the catheter, they were well out of their acute difficulties and easily managed their chronic condition by continuing to

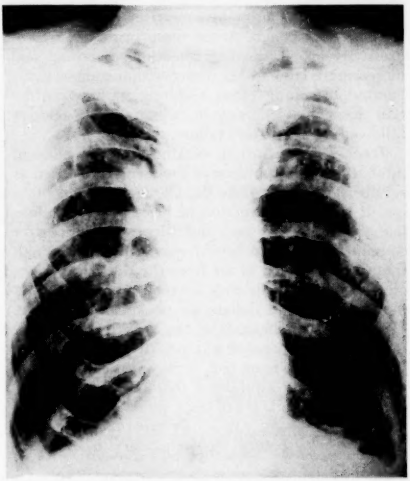


Fig. 4.—Chest roentgenogram of patient in case 4, showing severe fibrosis and emphysema.

intubate and aspirate as the need arose. This merely became a matter of acquiring the desired skill through daily practice.

Comment

The question naturally arises as to how tracheal fenestration relieves the symptoms of pulmonary insufficiency. We venture to offer an interpretation. The clinical course of a patient with low pulmonary reserve is characterized by recurrent attacks of what is best described as a "hypoventilation crisis." This may end either in sudden apnea and asphyxia or lead to slowly progressive cor pulmonale and cardiopulmonary failure. Patients who are tided over such attacks may be restored to a "status quo"

and continue to live within the limitations of their low pulmonary reserve until the next crisis arises. Mostly, however, each attack further diminishes cardiopulmonary reserve and brings the end nearer. Therefore, only by the prevention of such attacks can life be prolonged.

The evolution of these crises follows a characteristic clinical course which is due we believe to the following sequence of events: The attacks are usually precipitated by a complicating fresh respiratory infection (even a trivial catarrh), by oversedation, by excessive oxygen inhalation, or by a mild bout of congestive failure. Such circumstances generally bring on an increase of bronchial secretion. Failure to promptly eliminate this leads to stagnation, inspissation, and increased viscosity of secretions, resulting in progressive bronchiolar obstruction, increased air-trapping, and diminishing ventilation. The latter becomes further aggravated by persistent cough. All of these bring about progressive carbon dioxide retention, hypoxia, and increasingly labored breathing. Exhaustion in exaggerated breathing effort resulting in hypoventilation closes the vicious cycle, culminating in acidosis followed by congestive failure.

Tracheal fenestration, making possible efficient intubation and aspiration of the airways as often as is necessary, can reverse the above-described process. It relieves obstruction of bronchioles by elimination of secretions and decreases excessive coughing. It may relieve hypoventilation through frequent aspiration of air from the deeper airways, creating sharp expiratory currents which may act to untrap air and deflate air pockets in the lung. Treatment by fenestration can thus break the vicious cycle at any point and quickly bring the hypoventilation crisis to an end. It may also prevent such crises by timely aspirations that can keep the airways patent and ventilated, thereby forestalling provocative events. Obviously treatment must be applied early, before the pulmonary reserve becomes too low.

Clinical observations indicate that when the airways are kept clear and well ventilated, patients may continue to live within the limitations imposed by a low pulmonary reserve even when the latter seems from x-ray appearances to be so low as to make it difficult to believe. The concept of pulmonary reserve is too complex a problem to discuss here. Recently [3] we postulated that this is not merely a matter of apparently available alveolocapillary surface but rather one of bronchioloalevolar structures performing their normal function, acting in correlation with air and blood flow. As yet we know very little about this function of the terminal lung structures, which depends on normal pressures of air and blood flow maintained in the alveoli and in the pulmonary arteriolocapillary bed. Clinical observations have led us to believe that by keeping the airways patent and ventilated, tracheal fenestration enables the functioning lung structures to operate to the limit of their compensatory capacity.

The question will naturally arise as to the omission of blood gas studies and breathing capacity tests on these patients. It should be obvious that the two patients described were in no condition to perform any sort of breathing tests before operation. Furthermore, as their exercise tolerance was practically nil, there seemed to be no need for blood gas analyses. A few weeks after treatment, their exercise tolerance increased so remarkably that again there appeared to be no need for such tests. However, functional studies are now to be made by us on patients operated on in earlier phases of pulmonary insufficiency.

Last but not least in importance are the great advantages of tracheal fenestration in inhalation therapy. Mention was made above of the fact that mechanical ventilators, assistor as well as controller types, are operated more efficiently by way of intratracheal tubes than by way of masks (over the mouth and nose). For this reason tracheostomy is now being resorted to even when these machines are to be used for only short periods of time (days or weeks). In cases when we are dealing with fixed low pulmonary reserve where mechanical ventilatory aids are required for daily treatments permanently (as intermittent positive pressure breathing machines are now used in emphysema), tracheal fenestration obviously offers very great advantages. Similarly inhalation of bronchodilator and of detergent aerosols is far more efficient by the direct way of intratracheal tubes than by way of oral or intranasal insufflation.

The fact will not have escaped attention that, in the cases reported above, although the patients were in rather far-advanced stages of pulmonary insufficiency, no inhalation therapy of any sort was required after tracheal fenestration, and thorough aspiration of bronchial secretions was practiced during and after this procedure. Indeed, the fact that we could so dispense with the use of inhalation therapy as soon as thorough frequent aspiration became feasible is, we believe, further proof of the remarkable efficacy of tracheal fenestration in the management of progressive pulmonary insufficiency.

Summary

We propose tracheal fenestration as a new method of treatment in the management of advanced pulmonary insufficiency. It is a form of therapy that has developed as a result of long-range clinical observations. The following significant facts stand out: As pulmonary reserve diminishes patients become increasingly sensitive to the least interference with the patency and free flow of air in the airways of their lungs. With progression of pulmonary insufficiency, there arises the need for an early and permanent tracheal opening which per-

mits intubation and aspiration of the deeper airways as often as necessary. Intubation and aspiration of the deeper airways as required in the individual case is an effective method of relieving hypoventilation crises. Furthermore it appears to be the best method of preventing such crises in progressive pulmonary insufficiency.

Tracheal fenestration provides a permanent access to the deeper airways, which can be kept open or closed at will. Tracheal fenestration has so far been performed in too few cases and the clinical observations are still too recent for a final statement to be made. However, we believe this preliminary report is justified by the strikingly favorable results obtained.

Addendum

To date Dr. E. E. Rockey has performed tracheal fenestration on four additional patients with emphysema under practically the same conditions. The immediate relief from symptoms was equally striking, and the clinical results so far have been uniformly favorable.

850 Fifth Ave. (21) (Dr. Mayer).

References

1. Bendixen, H. H.: Discussion, Cases from Medical Grand Rounds: Massachusetts General Hospital: Case 394: Treatment of Ventilatory Insufficiency, Am. Pract. & Digest Treat. **9**:105-108 (Jan.) 1958.

2. Rockey, E. E.; Mayer, E.; and Rappaport, I.: Tracheal Fenestration: Experimental Aspect, Dis. Chest **30**:224-227 (Aug.) 1956. Rockey, E. E.: Surgical Technic of Tracheal Fenestration, Am. J. Surg. **94**:486-489 (Sept.) 1957. Rockey, E. E., and others: Tracheal Fenestration as New Method for Therapeutic Management of Pulmonary Diseases and for Experimental Exploration of Bronchial Tree, Bull. New York M. Coll., to be published.

3. Rappaport, I., and Mayer, E.: Changing Forms and Causes of Pulmonary Insufficiency in Present Era of Medicine, J. A. M. A. **165**:431-436 (Oct. 5) 1957.

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DIFFUSE GLOMERULONEPHRITIS AS A COMPLICATION OF SUBACUTE BACTERIAL ENDOCARDITIS

Frank B. Flood, M.D.
and
Raymond J. Boller, M.D., New York

A patient with a long history of abdominal surgery and recurrent fevers finally exhibited gross hematuria, oliguria, nitrogen retention, and other symptoms and signs of uremia. Before death a loud pericardial rub was noted and a severe melena appeared. Significant findings at autopsy were limited to the heart, kidneys, and cecum; the diagnoses were subacute vegetative endocarditis superimposed on an old rheumatic valvulitis, petechiasis of the cecum, and subacute diffuse glomerulonephritis. Diffuse glomerulonephritis is relatively infrequent as a complication of subacute bacterial endocarditis.

Diffuse proliferative glomerulonephritis is an unusual complication of subacute bacterial endocarditis. In an analysis of 52 proved cases of subacute bacterial endocarditis, Newman and coworkers [1] found only one case of diffuse glomerulonephritis, although 8 cases showed evidence of renal insufficiency. Baehr [2] reported 9 cases of diffuse glomerulonephritis in 77 cases of subacute bacterial endocarditis.

It is the purpose of this paper to present a case of subacute bacterial endocarditis in which diffuse proliferative glomerulonephritis, terminating in uremia, occurred. Of note is the fact that blood cultures, including anaerobic studies and bone marrow and postmortem left ventricular aspiration, were all sterile.

Report of a Case

A 58-year-old female entered St. Vincent's Hospital on Feb. 2, 1957, complaining of low abdominal cramps, burning on urination, left flank pain, and fever of two months' duration. The patient had been in relatively good health until Dec. 5, 1956, when shaking, chills, and fever developed 10 days after a sore throat. Under a short course of penicillin therapy, the patient's throat infection had cleared, but eight days later, fever (104 F [40 C]) and nausea occurred, and the patient was admitted to the hospital.

The patient had been followed by one of us (R. J. B.) since 1948, at which time a loud harsh systolic murmur, heard best along the left sternal border, was noted. The patient volunteered, at that time, that she had had "a

From the Medical Service, St. Vincent's Hospital of the City of New York.

murmur all of her life." There was no history of rheumatic fever. Chest x-rays showed normal cardiac dimensions. Electrocardiograms revealed no abnormalities and numerous urinalyses and complete blood cell counts were normal except for a slight to moderate anemia with hemoglobin level of 9 to 12 Gm. per 100 cc. The patient had undergone numerous surgical procedures between 1923 and 1940, including appendectomy, hemorrhoidectomy, cholecystectomy, hysterectomy (fibroid uterus), intestinal obstruction due to abdominal adhesions, and repair of umbilical hernia.

On admission in December, 1956, the patient appeared thin and had a temperature of 101.2 F (38.4 C). The blood pressure level was 120/80 mm. Hg, pulse rate was 112 per minute and regular, and a grade 3 apical systolic murmur was heard. There was no cardiomegaly. Abdominal examination showed left costovertebral angle tenderness. X-ray examination of the chest was unrevealing. Electrocardiography was normal, except for prominent, peaked P waves in leads 2, 3, and aVF. Urinalysis showed 2 + albuminuria, 1 to 2 red blood cells and 4 to 5 white blood cells per high-power field. There were no casts. The blood urea nitrogen level was 19 mg. per 100 cc. Urine culture grew out colonaerogens and Proteus organisms sensitive to chloramphenicol. Three blood cultures were negative. The patient was given chloramphenicol, 250 mg. four times a day by the oral route, became afebrile and asymptomatic, and was discharged on Dec. 19, 1956, the 15th hospital day. However, 10 days later, the patient was readmitted to the hospital with a return of fever and left flank pain. Physical findings were identical to the first hospital visit. Intravenous pyelography revealed a bifid right renal pelvis with partial reduplication of the right intrarenal elements. Cystography and retrograde pyelography disclosed a trigonitis and were suggestive of a right pyelonephritis. Urinalyses were normal, but urine culture showed vast numbers of Proteus organisms. A blood culture was sterile. Chloramphenicol therapy was reinstituted, with gradual response. The patient was discharged 20 days later, Jan. 19, 1957, after sterile urine cultures were obtained.

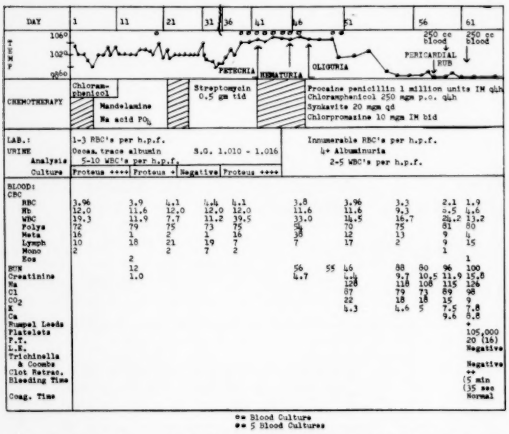

Fig. 1.—Clinical course and laboratory data during patient's final admission.

On admission, the patient was given penicillin, one million units intramuscularly every four hours, and chloramphenicol, 250 mg. every four hours, and the patient gradually became and remained afebrile. The clinical picture of uremia supervened and a loud pericardial friction rub was noted six days prior to her death. The blood and pulse pressures rose to 150/60 mm. Hg and remained at that level. Terminally, melena and severe anemia developed, and after a large amount of tarry liquid material was passed by rectum, the patient died.

During the final two weeks, severe left upper quadrant tenderness had developed. However, there was no palpable spleen. No definite alteration in heart murmurs was noted during her hospital course; nor did Roth's spots or Janeway's spots appear. Figure 1 outlines the hospital course during her final admission.

Autopsy Findings.—Autopsy findings of significance were limited to the heart, kidneys, and cecum. The heart weighed 280 Gm. There were many fine filamentous bands between the pericardium and epicardium. The latter was roughened. The mitral valve measured 9 cm. in circumference. The leaflets were rolled and thickened and the chordae tendineae were short and thick. The papillary musculature was hypertrophied. On the posterior leaflet of the mitral valve, at the lateral junction of the posterior and anterior leaflet, was found a firmly attached 0.5-by-0.6-cm. raised greenish-brown papillary protrusion. Miscroscopic examination of the mitral valve revealed the cusp to be diffusely thickened due to fibrosis. The fibrous tissue was dense and hyalinized. At one point, the cusp was ulcerated and covered with a bulky mass of deeply eosinophilic fibrin material. Diagnosis: subacute vegetative endocarditis superimposed on an old rheumatic valvulitis.

The kidneys grossly demonstrated innumerable small dark-red punctate areas over the external surface. These were also scattered throughout the renal parenchyma. The external surfaces were smooth, with grey-white capsules which stripped easily. The right kidney weighed 220 Gm., the left 200 Gm. The calyces, pelves, ureters, and bladder were entirely normal. Microscopic section revealed involvement of all glomeruli (fig. 2). Some showed simple swelling of the epithelial cells, obliterating the lumen of glomerular capillaries rendering them ischemic. Other glomeruli demonstrated typical crescent formations. A large number of glomeruli contained fibrinous thrombi. Numerous tubules were distended with red blood cells. Diagnosis: subacute diffuse glomerulonephritis.

The cecum grossly presented many small punctate hemorrhagic areas in the submucosa. The external surface, however, appeared normal. Diagnosis: petechiasis of cecum.

Comment

It certainly would appear reasonable to assume that, in following a case of subacute bacterial endocarditis with complicating renal insufficiency, the exact pathological process in the kidney could

Fig. 2.—Microscopic section of kidney demonstrating diffuse glomerulonephritis.

be foreseen by the severity of the renal insufficiency. When true uremia becomes manifest clinically, the presence of a diffuse glomerulonephritis should be suspected. This is in contradistinction to the renal insufficiency, usually less severe, seen in focal embolic glomerulonephritis. Combinations of both types of glomerular disease may occur. Friedberg [3] states that four types of renal lesions may occur in subacute bacterial endocarditis: (1) focal embolic glomerulonephritis; (2) diffuse glomerulonephritis (which our case demonstrates); (3) renal infarction; and (4) combinations of the first three.

No indisputable evidence has been presented to date to explain why one person with subacute bacterial endocarditis may develop any of the above renal lesions singly or in combination. Several years ago, Lillehei and co-workers,[4] in a series of experiments on dogs in whom large arteriovenous fistulas were constructed, were able to induce bacterial endocarditis in 100% of the animals by the intravenous introduction of small numbers of bacteria, although no cases occurred in animals without fistulas. Furthermore, 40% of the infected dogs developed acute proliferative glomerulonephritis in a week to five months after endocarditis occurred. These workers postulated that endothelial susceptibility was created in the heart and the kidneys by "cardiovascular stress." Certainly further work as to the more precise nature of this interesting corelationship remains to be done.

Summary

The occurrence of diffuse glomerulonephritis as a complication of subacute bacterial endocarditis is relatively infrequent. Focal embolic glomerulonephritis, diffuse glomerulonephritis, renal infarction, or combinations of these three types of lesions may occur as complications of subacute bacterial endocarditis. The precise nature of the corelationship of diffuse glomerulonephritis and subacute bacterial endocarditis remains to be established.

30 E. 40th St. (16) (Dr. Boller).

References

1. Newman, W.; Torres, J. M.; and Guck, J. K.: Bacterial Endocarditis: Analysis of 52 Cases, Am. J. Med. **16**:535-542 (April) 1954.

2. Boyd, W.: Pathology of Internal Diseases, ed. 5, Philadelphia, Lea & Febiger, 1950.

3. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1949, p. 783.

4. Lillehei, L. W., and others: Role of Cardiovascular Stress in Pathogenesis of Endocarditis and Glomerulonephritis: Observations Including Method of Experimental Production Utilizing Arteriovenous Fistulas, A. M. A. Arch. Surg. **63**:421-434 (Oct.) 1951.

DIAGNOSTIC VIROLOGY.—The rapidly expanding field of cellular virology has applied as well as fundamental scientific value. Practical applications of cell culture are helpful to the physician and to the epidemiologist (and indirectly, to the average citizen) for isolation of viruses and accurate assessment of individual or group immunity. The specific diagnosis of poliomyelitis, for example, and of many other virus infections is accomplished readily by cell-cultural methods. Virus is isolated and recognized by its ability to affect and destroy susceptible cells in culture, while the capacity of homotypic antibody to neutralize cytopathogenic potential of the virus permits identification of isolates. Cell cultures bring diagnostic virology within reach of all laboratories and offer reliable results obtainable almost as quickly as those required for diagnosis of other microbial infections.—J. T. Syverton, M.D., The Response of Mammalian Cells in Culture to Virus Infection, *Decennial Review Conference on Tissue Culture*, Oct. 8-12, 1956.

CLINICAL EXPERIENCES WITH WARFARIN (COUMADIN) SODIUM AS AN ANTICOAGULANT

Samuel Baer, M.D., M. William Yarrow, M.D., Charles Kravitz, M.D.
and
Victor Markson, M.D., Philadelphia

Coumadin sodium and bishydroxycoumarin were used in a study of the effects of anticoagulant therapy on 200 patients, most of them with acute myocardial infarction or severe coronary insufficiency. Coumadin sodium was given orally to 164 of these patients, the prothrombin times being determined daily. Individual dosages were adjusted until the daily dose (usually 5 to 7.5 mg.) needed to maintain the prothrombin level between 15% and 30% was found. Bishydroxycoumarin was given to 19 patients and dosages were similarly adjusted until the maintenance dose (between 20 and 100 mg. daily) was found. An additional group of 17 patients who at first received bishydroxycoumarin were shifted to therapy with coumadin sodium. Coumadin sodium was found to be far superior to bishydroxycoumarin. Coumadin sodium had the advantage of greater promptness of effect; it produced the desired prothrombin levels within 48 hours in 87% of the cases. Patients receiving it in maintenance doses were more likely to stay within the desired range of prothrombin levels. The frequency of side-effects (mainly hemorrhagic) was slightly though not significantly lower in the patients treated with coumadin sodium. Nine patients who exhibited bleeding phenomena promptly responded to withdrawal of the coumadin sodium or treatment with preparations of vitamin K.

A voluminous and, at times, controversial literature has accumulated during the past 15 years concerning the use of anticoagulant therapy in clinical medicine. Widespread interest in the use of anticoagulants for the treatment of acute myocardial infarction resulted from the early studies on bishydroxycoumarin (Dicumarol) both in the United States and abroad. A detailed study was begun in the United States by Dr. Irving Wright and the cooperative study group of the American Heart Association.[1] The varied opinions expressed [2] on the value of anticoagulants indicate that their routine use in acute myocardial infarction is by no means settled.

We have felt for some time that much of this uncertainty stemmed from difficulties encountered in using bishydroxycoumarin. The necessity for rigid laboratory control and daily or almost daily prothrombin time determinations, the unpredictability or the extent of the hypoprothrombinemic response resulting from a fixed initial dose of bishydroxycoumarin, the uncertain degree of intestinal absorption of the drug, the rather appreciable expense resulting from daily prothrombin determinations—all these factors helped generate differences of opinion concerning many aspects of anticoagulant therapy. We have been continuously interested, therefore, in attempts to find a more satisfactory anticoagulant for oral administration.

Recently a number of anticoagulant drugs have been introduced that offered some promise of being superior to bishydroxycoumarin. One that seemed to more nearly approach the ideal orally given anticoagulant than any of those previously described was warfarin (Coumadin) sodium. This is a report of observations in 200 patients treated at the Albert Einstein Medical Center, Philadelphia, with warfarin sodium or bishydroxycoumarin. Of the patients forming the basis of this study, 171 had acute myocardial infarction or severe coronary insufficiency, 6 had congestive heart failure, and 23 had phlebitis or some other thromboembolic disturbance.

Method

Of the 200 patients in this study, 164 were placed on orally administered warfarin sodium therapy. An initial dose of 1 mg. per kilogram of body weight was given, but we soon found it was not always practical to weigh patients. We then administered an initial dose of 60 to 75 mg., depending on the estimated size of the patient. A prothrombin time determination (by the Quick method) was obtained prior to the first administration of warfarin. Prothrombin times were then determined daily. Successive doses of warfarin sodium were varied with the daily prothrombin time, with use of the following schedule as a guide: (1) below 10%, no warfarin; (2) 10-19%, 2.5-5 mg.; (3) 20-29%, 5-10 mg.; (4) 30-39%, 10-15 mg.; and (5) above 40%, 20 mg. or more.

Experience soon led us to judge in each case the daily dose (usually 5-7.5 mg.) necessary to maintain the prothrombin level between 15% and 30%. Wherever possible, the warfarin was administered in the early afternoon after the day's prothrombin times were obtained. All prothrombin times were determined in the hospital laboratory. A total of 164 patients were treated with warfarin for 4 to 46 days. During this same time, 19 patients receiving

Senior Attending Physician (Dr. Baer), Adjunct (Dr. Yarrow), Associate (Dr. Kravitz), and Resident (Dr. Markson), the Department of Medicine, Albert Einstein Medical Center.

Read before the 11th Clinical Meeting of the American Medical Association, Philadelphia, Dec. 6, 1957.

bishydroxycoumarin were followed and, in addition, 17 patients begun on bishydroxycoumarin therapy were transferred to warfarin sodium therapy. Patients treated with bishydroxycoumarin were begun on 200 to 300 mg. and then given maintenance doses varying between 20 and 100 mg. daily.

Results

Our observations related primarily to four major aspects of anticoagulant therapy. One was the frequency and rapidity with which therapeutic hypoprothrombinemia was obtained after the initial dose of warfarin sodium. The second aspect of the study concerned the length of time necessary to reach therapeutic levels, which we considered to be between 15% and 30% of normal. The determination of the number of days that the prothrombin time remained within therapeutic levels and the dose necessary to maintain this level was a third essential consideration. Finally, we were concerned with the possibility of untoward reactions and the extension of pharmacological activity.

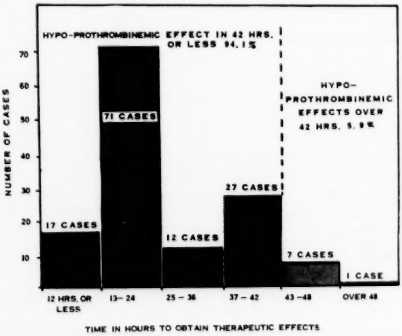

Fig. 1.—Beginning hypoprothrombinemic effect obtained with warfarin sodium therapy (135 patients).

These various aspects of warfarin therapy were evaluated in 181 patients, 17 of whom received both warfarin and bishydroxycoumarin. In 135 of the 164 patients receiving warfarin alone, we were able to determine the approximate time in hours from the administration of the drug to beginning therapeutic effects (fig. 1). In 88 patients (65%), hypoprothrombinemic effects were obtained in 24 hours or less and 94% exhibited therapeutic effects in 42 hours or less. This aspect of warfarin sodium therapy was actually evaluated in retrospect. Shapiro [3] has shown that many of his patients revealed beginning depression of prothrombin times within 8 to 12 hours of an initial oral dose of warfarin. In 141 of our cases we were able to determine the time necessary to reach the established therapeutic level, 15%-30% (fig. 2 and 3). In 123 cases (87%), true therapeutic levels were obtained in 48 hours or less. This is in sharp contrast to levels achieved with bishydroxycoumarin, which frequently requires 60 to 96 hours. In only one case, that of a patient with myocardial infarction and narcotic addiction, were we unable to reach therapeutic levels despite massive doses of warfarin.

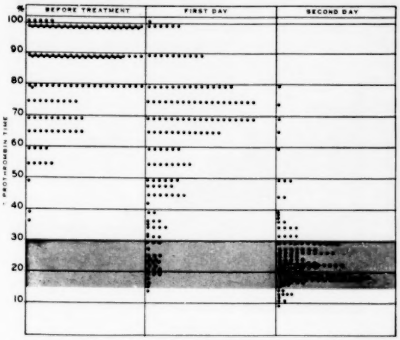

Fig. 2.—Depression of prothrombin time to therapeutic levels with warfarin sodium. (Each dot represents one patient.)

One of the disturbing aspects of bishydroxycoumarin therapy has been the frequency and unpredictability with which patients receiving this drug escape from therapeutic range. We found that only one-third of the 36 patients receiving bishydroxycoumarin were within therapeutic range 70-100% of the time; 22 patients (66.7%) were within therapeutic range less than 70% of the time (fig. 4). In contrast to this, we found that 132 (83.5%) of the 158 patients receiving warfarin for more than four days were within therapeutic range 70% or more of the time (fig. 5).

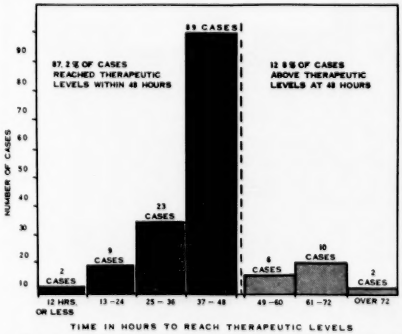

Fig. 3.—Time necessary to reach full therapeutic levels of prothrombin time with warfarin sodium (141 patients).

Toxicity and Untoward Reactions

Of the 19 patients receiving bishydroxycoumarin alone, 4 had untoward reactions. In two patients there was microscopic hematuria, in one rectal

bleeding, and in one an unexplained fall in hemoglobin and hematocrit levels. The hematuria in both cases quickly disappeared as the dose of bishydroxycoumarin was decreased. In the patient with bleeding, a carcinoma of the colon was demon-

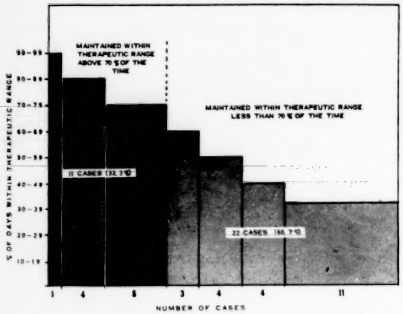
MAINTAINED WITHIN THERAPEUTIC RANGE ABOVE 70 % OF THE TIME
MAINTAINED WITHIN THERAPEUTIC RANGE LESS THAN 70 % OF THE TIME
11 CASES (33.3%)
22 CASES (66.7%)
% OF DAYS WITHIN THERAPEUTIC RANGE
NUMBER OF CASES

Fig. 4.—Days within therapeutic range with bishydroxycoumarin (33 patients).

strated. In the last case, there was no explanation for the fall in hemoglobin level, despite continued search for blood loss. Of the 181 patients receiving warfarin sodium, 9 exhibited bleeding phenomena as an extension of pharmacological effect. Three had gastrointestinal bleeding, two had bleeding gums or bloody sputum, one had hematuria, one had epistaxis, one had menorrhagia, and one had cutaneous petechiae. In the patients with gastrointestinal bleeding, we were able to demonstrate a

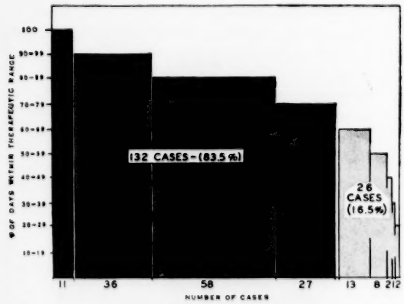

Fig. 5.—Days within therapeutic range with warfarin sodium (158 patients).

benign antral ulcer, bleeding hemorrhoids, and carcinoma of the lung respectively. In eight of these nine cases with hemorrhagic complications, the prothrombin times were below 20% and bleeding promptly ceased when the warfarin was withdrawn or vitamin K or K_1 oxide was administered.

Comment

Extensive investigation firmly established the value of bishydroxycoumarin (Dicumarol) as the first effective orally given anticoagulant. However, objections and difficulties encountered in its use led to continued search for a more satisfactory anticoagulant. Ethyl biscoumacetate and cyclocumarol, two of the earlier coumarin derivatives, seemed superior in some ways to bishydroxycoumarin. Nonetheless, their use was attended by sufficient objections to prevent their widespread adoption as the "ideal anticoagulant."

The continued investigation of synthetic derivatives of bishydroxycoumarin by Link and his colleagues led to the development of warfarin sodium. (The recently introduced synthetic acenocoumarin investigated by Neill and others,[4] Manchester,[5] and Alexander and others[6] seems to have an almost identical chemical formula and quite similar hypoprothrombinemic effects.)

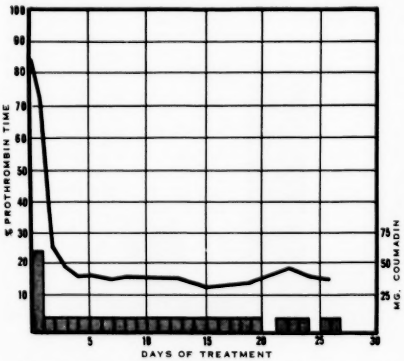

Fig. 6.—Levels of prothrombin time over 26 days in patient treated with warfarin sodium.

Our experience with warfarin has demonstrated its many advantages over bishydroxycoumarin. Pollock,[7] Clatanoff and others,[8] Shapiro,[3] and Goodman[9] have also suggested that warfarin more nearly approaches the ideal anticoagulant than any available drug to date. If the initial dose is adequate and given in one dose as recommended and if prothrombin levels are carefully followed in relation to the first administration of warfarin, therapeutic hypoprothrombinemia should be obtained in at least 95% of patients. Furthermore, the prothrombin level will be depressed to the therapeutic range of 15% to 30%, in 90% of the cases, in 42 hours or less. We found that the great majority of the 12.8% of our patients who required more than 48 hours to attain therapeutic levels had not received adequate amounts of warfarin the first or second day. Another distinct advantage of warfarin is the predictability of response and the ease with which the prothrombin level is maintained almost

constantly and with very little fluctuation within therapeutic range. Figures 6 and 7 illustrate the smooth level of prothrombin times obtained in a patient with warfarin, in contrast to the variable levels obtained in another patient with bishydroxy-

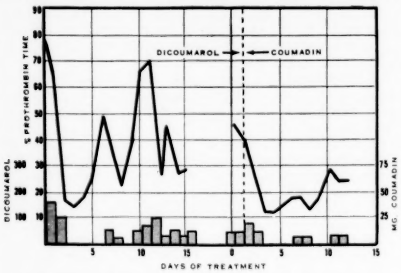

Fig. 7.–Levels of prothrombin time in patient treated with bishydroxycoumarin.

coumarin. Prothrombin time tests done at the same time each day and the administration at a scheduled time of the day of the appropriate dose of warfarin, based on the results of the test, facilitate the ease with which the level is maintained within therapeutic range. Once the physician has gained experience in the use of warfarin sodium and the patient's pattern of prothrombin depression response to it is established, one can safely decrease the daily measurement of prothrombin times in the hospital to every second, third, or fourth day (fig. 8).

Our studies did not specifically include measurements of the time required for prothrombin levels to return to normal when warfarin sodium therapy was discontinued. However, Shapiro,[6] Pollock,[7] and other observers have demonstrated that hypoprothrombinemia after one dose of 75 to 100 mg. of warfarin will persist for two to five days. In those cases in which rapid elevation of the prothrombin level is desired, we have had no difficulty in mitigating warfarin effect by restoring the prothrombin time to at least 70% within 6 to 12 hours with whole blood, vitamin K, or vitamin K_1 oxide therapy.

One other aspect of anticoagulant therapy merits discussion. Little is yet known concerning the mechanism underlying the pathogenesis of atherosclerosis and vascular thrombosis. It is quite possible that disturbances in the clotting mechanism may play as important a part in the development of coronary thrombosis as disorders of fat and cholesterol metabolism. A number of studies in Norway and Russia during the last war suggested that when the caloric and fat intake were increased after relief of the blockade there was a fairly prompt increase in thromboembolic disturbances of all types. If there is any merit to these and related observations, there is then a logical basis for considering the value of long-term anticoagulant therapy. Warfarin sodium seems an ideal preparation for this purpose. Is this anticoagulant of any value in the long-term treatment of severe angina pectoris? Can it help retard the atherosclerotic process? Can it prevent recurrent coronary thrombosis and myocardial infarction? These questions are intriguing ones. Some studies with these thoughts in mind have already been published by Manchester and Putnam,[5] with use of acenocoumarin, and by a number of observers, with use of bishydroxycoumarin or one of its analogues. In our preliminary evaluation of long-continued warfarin therapy, we have easily maintained therapeutic hypoprothrombinemia in a number of outpatients, determining the prothrombin time at intervals of 10 to 20 days and using maintenance doses of 5 to 10 mg. of warfarin daily. We are now engaged in the further evaluation of long-term anticoagulant therapy in the prevention of coronary thrombosis and other thromboembolic disturbances in a larger series of ambulatory patients.

Summary

Hypoprothrombinemic properties of warfarin (Coumadin) sodium and bishydroxycoumarin (Dicumarol) were evaluated in 200 patients. Beginning therapeutic effect was accurately determined in 135 patients receiving warfarin; 65% exhibited therapeutic effects in 24 hours or less, and in 42 hours 94% exhibited beginning therapeutic effects. The time necessary to reach true therapeutic levels with warfarin was measured in 141 patients. In 123 (87%) true therapeutic levels of 15% to 30% were reached in 48 hours.

Of all patients receiving warfarin, 132 (83.5%) were within therapeutic range 70% of the time or more. This is in sharp contrast to results with

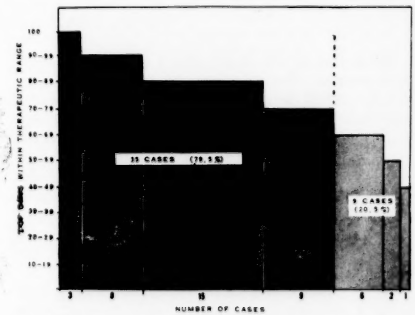

Fig. 8.–Days within therapeutic range with warfarin sodium, with intermittent prothrombin time determinations (44 patients).

bishydroxycoumarin; only 33.3% of these patients were within therapeutic range at least 70% of the period of observation.

The drug was easy to use, and prothrombin times were readily and smoothly controlled with small daily maintenance doses. There were no important

side-effects, and the nine patients who exhibited bleeding phenomena promptly responded to administration of whole blood and vitamin K or K_1 oxide. Experiences in this study give further confirmatory evidence that warfarin is far superior as an anticoagulant to bishydroxycoumarin and that it most closely approaches the "ideal anticoagulant."

5123 N. Broad St. (41) (Dr. Baer).

The warfarin sodium used in this study was provided by Dr. Edward Barrett, medical director, Endo Laboratories, Inc., Richmond Hill, N. Y., as Coumadin sodium in 5, 10, and 25 mg. tablets.

References

1. Wright, I. S.; Marple, C. D.; and Beck, D. F.: Report of Committee for Evaluation of Anticoagulants in Treatment of Coronary Thrombosis with Myocardial Infarction (Progress Report on Statistical Analysis of First 800 Cases Studied by This Committee, Am. Heart J. **36:**801-815 (Dec.) 1948. Wright, I. S.: Modern Treatment of Coronary Thrombosis with Myocardial Infarction, Circulation **2:**929-936 (Dec.) 1950.

2. Rytand, D. A.: Anticoagulants in Coronary Thrombosis with Myocardial Infarction, A. M. A. Arch. Int. Med. **88:**207-210 (Aug.) 1951. Russek, H. I.; Zohman, B. L.; White, L. G.; and Doerner, A. A.: Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction, J. A. M. A. **145:**390-392 (Feb. 10) 1951. Baer, S.; Heine, W. I.; and Krasnoff, S. O.: Mortality of Acute Myocardial Infarction in Private Practice, Am. J. M. Sc. **222:**500-505 (Nov.) 1951. Baer, S.; Krasnoff, S. O.; and Heine, W. I.: Criteria for Use of Anticoagulants in Acute Myocardial Infarction, Pennsylvania M. J. **56:**274-278 (April) 1953.

3. Shapiro, S., and Gordon, S. M.: What Anticoagulant Shall I Use? Scientific Exhibit, presented at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955. Shapiro, S.: Anti-coagulant Therapy, S. Clin. North America **36:**469-483 (April) 1956.

4. Neill, E. C.; Moon, R. Y.; and Vander Veer, J. B.: Clinical Evaluation of New Anticoagulant "Sintrom," Circulation **15:**713-720 (May) 1957.

5. Manchester, B., and Putnam, L. E.: New Antithrombotic Agent, Scientific Exhibit, presented at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.

6. Alexander, F.; Koppel, J. L.; Arscott, P. M.; and Olwin, J. R.: Clinical Experience with Anticoagulant Acenocoumarin (Sintrom), A. M. A. Arch. Int. Med. **100:**558-564 (Oct.) 1957.

7. Pollock, B. E.: Clinical Experience with Warfarin (Coumadin) Sodium, New Anticoagulant, J. A. M. A. **159:**1094-1097 (Nov. 12) 1955; Early Management of Myocardial Infarction, ibid. **161:**404-409 (June 2) 1956.

8. Clatanoff, D. V.; Triggs, P. O.; and Meyer, O. O.: Clinical Experience with Coumarin Anti-coagulants Warfarin and Warfarin Sodium, A. M. A. Arch. Int. Med. **94:**213-220 (Aug.) 1954. Clatanoff, D. V., and Meyer, O. O.: Further Observations on Use of Warfarin Sodium in Anticoagulant Therapy, ibid. **97:**753-757 (June) 1956.

9. Goodman, D. H.: Experience with New Anticoagulant Coumadin (Warfarin) Sodium, Arizona Med. **13:**389-392 (Oct.) 1956.

TREATMENT OF ALLERGIC RESPONSE TO PENICILLIN

PRELIMINARY REPORT

Frank O. Warren, M.D., Manchester, N. H.

Manifestations of allergy to penicillin, ranging from a mild rash with itching to giant urticaria and polyarthritis, were seen in 10 patients. In four of these the penicillin had been given prophylactically in connection with surgery. Medication consisting of 300 mg. of potassium salicylate, 300 mg. of sodium p-aminobenzoate, and 50 mg. of ascorbic acid, in the form of tablets given four times a day, completely relieved the allergic symptoms within 24 to 48 hours in nine of the patients. The 10th patient, who had had severe general reactions to a preparation of penicillin in the past, was enabled to take the same preparation without allergic reaction by taking the above medication prophylactically at the same time. Its use is still empirical, since it is not yet known which of the ingredients are active and how they interact, and further investigation is recommended.

Since the advent of the use of penicillin in medical practice, the development of an allergic response to this drug has not been uncommon. These reactions have varied from a mild erythematous eruption with severe itching to giant urticarial wheals and, in many cases, a polyarthritis of many months' duration. In the past, the treatment of this syndrome has been unsatisfactory. Antihistaminics are not as effective as might be wished; the steroids have been employed in some cases, but the use of these entails the risks which are inherent in any steroid therapy.

In an attempt to treat the polyarthritis associated with a penicillin reaction, a patient was given Pabalate (a composition of 300 mg. each of sodium salicylate and sodium *p*-aminobenzoate, with 50 mg. of ascorbic acid), one tablet four times a day. Within 48 hours, the arthritis, wheals, and hives which were present had completely disappeared. After a short period of time, the Pabalate therapy was discontinued and there was no reappearance of symptoms. This chain of events, except for the relief of the polyarthritis, was un-

expected, and therefore the therapy was tried in several other patients to determine whether there was a causal relationship. The response obtained was the same.

Mechanisms Involved in Relieving Allergic Response

It is of interest to consider briefly the mechanisms which may be involved in relief of the manifestation of penicillin sensitivity. It has been shown [1] that the administration of salicylate causes an elevation of the ACTH level in the blood, and in some animals a depletion of adrenal ascorbic acid is noted after the administration of about one-half the lethal dose of salicylates. It has been further reported by other authors [2] that the physiological response to salicylates is similar to the response to ACTH or cortisone. However, it has not been shown that the administration of salicylates causes any increased urinary excretion of adrenocortical steroids,[3] and indeed other workers [4] have stated that the antirheumatic effects of salicylates appear to be neither related to nor dependent upon elevated circulating levels of adrenal steroids. It has been suggested that they may be due to an enhanced ability of the tissues to utilize the steroids, although it is possible that salicylate action is in no way related to adrenal hormones. Some investigators have believed that such agents as aspirin may both exhibit a stimulating effect on the pituitary gland and effect an increase in the rate of removal of the steroids from the circulation by means other than urinary excretion.[5]

Zarafonetis [6] has published papers on the use of potassium *p*-aminobenzoate in the treatment of a variety of collagen diseases and in dermatitis herpetiformis. One patient with dermatitis herpetiformis reported in 1952 was treated with potassium *p*-aminobenzoate which caused an initial flare, followed by improvement of the pruritus, although the eruption remained virtually the same.[7] In 1952, 20 patients with various inflammatory skin diseases were given sodium *p*-aminobenzoate by mouth in daily doses ranging up to 16 Gm. for periods of two weeks to several months. Results were variable, but the authors[8] felt that they had achieved cures in some cases at least of atopic dermatitis and contact dermatitis and a transient response in a patient with dermatitis herpetiformis. In 1950, Ricci [8a] reported that orally given *p*-aminobenzoate caused an immediate therapeutic response in 34 infants and children suffering from serum sickness after the administration of diphtheria antitoxin. Five untreated patients used as controls experienced a more severe and prolonged illness.

Other authors have pointed out a synergistic action between *p*-aminobenzoic acid and salicylates, and it has been demonstrated that the concurrent administration of both agents increases the salicylate concentration in the blood above that which is achieved when the salicylate in the same dosage is administered alone.[9] Good and his associates [10] have demonstrated the ability of combined *p*-aminobenzoic acid and salicylate therapy to reduce from 90% to 10% the incidence of experimentally produced allergic acute disseminated encephalomyelitis in guinea pigs. Neither *p*-aminobenzoic acid nor salicylates alone gave this order of protection even when salicylate intoxication was induced.

The functions of vitamin C in the body are many and varied. Recently Reppert and co-workers [11] have drawn attention to the speed with which ascorbic acid corrects the capillary fragility in scurvy, and their work indicates that ascorbic acid in large doses inhibits the hyaluronidase–hyaluronic acid reaction and that this inhibition of the "spreading factor" may account for the rapid improvement noted. It has also been noted by Long and his associates [12] that orally given ascorbic acid desensitized BCG-infected guinea pigs to intradermally injected tuberculin. The role of vitamin C in adrenal function is still the subject of much investigation and question. However, it is apparent that an intimate relationship exists between vitamin C and the corticosteroids.[13]

From the preceding brief discussion, it can be readily seen that the activity of Pabalate in penicillin sensitivity may be theoretically ascribable to any one of the individual components. Due to the present widespread use of salicylates and ascorbic acid as contained in multiple vitamin preparations, it is more likely that the *p*-aminobenzoic acid plays a major role either alone or in synergism with one or more of the other components. This has yet to be established and will be the subject of future work.

Report of Cases

Case 1.—A 27-year-old male with no previous history of allergies underwent a rib resection for an osteochondroma, and the patient was placed on penicillin therapy postoperatively as a prophylactic measure. One week after penicillin therapy, he developed a polyarthritis that was characterized by remissions and exacerbations and that affected different joints at different times. He also developed hives, with moderate to severe itching. He was treated for a period of several weeks with antihistaminics, which had no effect. Pabalate, one tablet four times a day, was administered as therapy for the polyarthritis. Forty-eight hours later the patient returned to report that no further outbreaks of his arthritis had occurred and that, in addition, his wheals and hives had no longer been in evidence. From this point on, he was completely free of any symptoms of an allergic nature. In this instance it was felt that the Pabalate probably helped his arthritis, but no explanation could be given for the disappearance of the urticaria and hives.

Case 2.—A 47-year-old female was seen at her home with a generalized erythematous eruption and severe itching. Forty-eight hours previously she had received penicillin. She had a generalized edema of the face, and her periocular tissues were edematous, causing her palpebral slits to be markedly narrowed. A diagnosis of penicillin sensitivity was made. The patient was given Pabalate, one tablet four times a day. In 24 hours her itching had been relieved, and the rash had faded to about one-half of its former extent. Within 48 hours she was completely back to normal, with no further itching and no further rash. Therapy was discontinued in this case.

Case 3.—A 32-year-old man had been treated six months prior to examination with a course of penicillin. He developed a polyarthritis which was characterized by remissions and exacerbations, affecting different joints on each exacerbation. He had been treated at different times by the physician who had originally used the penicillin but had gained no relief from any of the drugs employed. He had learned from other patients that I had a "miracle cure" for this condition and hence called upon me. He was given Pabalate, one tablet four times a day. Forty-eight hours later he phoned to report that he had no further polyarthritis and was completely asymptomatic.

Case 4.—A 4-year-old boy received a severe laceration of the tongue, which was sutured with the patient under general anesthesia in the operating room. He was given penicillin orally as a prophylactic measure. Twenty-four hours postoperatively the mother phoned to report that the child had measles or poison ivy, as he had broken out with a severe erythematous rash and complained of severe itching. The mother was reassured that this was penicillin reaction and was advised to discontinue administration of penicillin. Four ounces of Pabalate liquid was prescribed, with directions to take one teaspoonful four times a day. The mother called 24 hours later to report that the rash had disappeared and that there was no further itching. Pabalate therapy was discontinued. The lad was seen in the office one week later, and he showed no further evidence of any reaction to the penicillin.

Case 5.—A 52-year-old woman was given penicillin prophylactically after a panhysterectomy. Her daughter, a trained nurse, telephoned on the patient's seventh postoperative day to state that her mother had urticarial wheals on her upper arms and chest. Pabalate, one tablet four times a day, was prescribed. Twenty-four hours after medication was instituted, the wheals disappeared and did not recur.

Case 6.—A 37-year-old female was treated for acute follicular tonsillitis. She was given Biosulfa 250 (a composition containing 250,000 units of crystalline potassium penicillin G, and 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine), and 48 hours after the institution of penicillin therapy she called to report an erythematous eruption with itching. The penicillin medication was discontinued and Pabalate, one tablet four times a day, was prescribed. Twenty-four hours after institution of Pabalate therapy the patient reported that the rash had disappeared and that she had no further itching or signs of an allergic reaction.

Case 7.—A 26-year-old female underwent a panhysterectomy, and penicillin injections were ordered prophylactically. Forty-eight hours postoperatively the patient developed an erythematous eruption and complained of itching. Penicillin therapy was discontinued. Pabalate, two tablets every four hours, was prescribed. After five doses of this medicament, the rash disappeared, the pruritus disappeared, and the patient had no further difficulty.

Case 8.—A 73-year-old woman had been given penicillin one week previously by another physician and developed a severe rash with itching. She was treated with antihistaminics to no avail. Pabalate, one tablet four times a day, was prescribed, and the patient reported complete relief in 48 hours.

Case 9.—A 29-year-old male was seen with acute follicular tonsillitis. He was advised that penicillin therapy would be the best regimen of treatment for this situation. He became quite alarmed because on two previous occasions he had been given penicillin and had broken out with hives accompanied by severe itching. He had been warned by his doctor to caution any physician in the future against administering penicillin to him. For the first time, the opportunity presented itself to institute Pabalate therapy prophylactically. The aforementioned cases were cited to him briefly and it was brought out that I desired to use Pabalate prophylactically to prevent an allergic response to penicillin. His cooperation was sought and he agreed to try it. Penicillin was given orally in the form of Biosulfa 250 and also Pabalate, one tablet four times a day, to be taken concurrently with the other medicament. During the course of treatment, no evidence of allergy developed nor did any allergy develop after medication was discontinued.

Case 10.—A 21-year-old female was seen with acute follicular tonsillitis. Eighteen months previously she had been treated with penicillin and had developed a severe, generalized erythema and urticaria. At that time she had been treated also with Pabalate, with remission of her symptoms in 24 hours. It was requested that she take penicillin and the drug that had relieved her of her symptoms previously. She was reassured that in all probability an allergic reaction would not develop when both drugs were taken simultaneously. She agreed to try it and was given Biosulfa 250, the product to which she had been allergic previously, and Pabalate, one tablet four times a day, to take at the same time. During her course of therapy, no reaction occurred to the penicillin, and there were no allergic responses after treatment was discontinued.

Summary

Pabalate (a composition of 300 mg. each of sodium salicylate and sodium *p*-aminobenzoate, with 50 mg. of ascorbic acid) has been used in the treatment of penicillin sensitivity reactions. It is impossible to say at this time whether a single component is the active material or whether there is a synergistic action between two or more of the compounds included in the formulation. The use of Pabalate in the treatment of penicillin sensitivity reactions warrants further investigation.

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References

1. Eades, C. H., Jr., and King, J. S., Jr.: Detectable Amounts of ACTH in Blood Following Salicylate Administration, Endocrinology **52**:594-596 (May) 1953.

2. Kelley, V. C.: Role of Pituitary-Adrenal System in Rheumatic Fever, Journal-Lancet **75**:291-308 (July) 1955.

3. Smith, M. J. H.; Gray, C. H.; and Lunnon, J. B.: Urinary Excretion of Adrenocortical Steroids by Patients Receiving Salicylates, Lancet **1**:1008-1009 (May 15) 1954.

4. Kelley, V. C.: Dual Action of Salicylates in Relation to Adrenal Function: Implications in Thearpy of Rheumatic Diseases, read before the First Pan American Congress on Rheumatic Diseases, Rio de Janeiro and Sao Paulo, Brazil, Aug. 15, 1955.

5. Done, A. K.: American Rheumatism Association, Annual Interim Scientific Session, abstracted, What's Happening in Medicine, Postgrad. Med. **19**: facing A-32 (Feb.) 1956.

6. Zarafonetis, C. J. D.; Steiger, W. A.; Ginsburg, I. W.; and Heather, A. J.: Treatment of Rheumatoid Arthritis with *P*-aminobenzoate and Acetylsalicylic Acid, A. M. A. Arch. Int. Med. **92**:204-215 (Aug.) 1953. Zarafonetis, C. J. D., and Shaw, J.: Treatment of Pemphigus with Potassium Paraaminobenzoate, abstracted, J. Clin. Invest. **31**:674 (June) 1952.

7. Friedman, R.; Weiner, J.; Gorpen, J.; and Zarafonetis, C. J. D.: Dermatitis Herpetiformis, A. M. A. Arch. Dermat. **65**:637-638 (May) 1952.

8. Grayson, L. D., and Steiner, K.: Sodium Para-aminobenzoate ("PABA") in Treatment of Dermatoses, J. Invest. Dermat. **19:**463-466 (Dec.) 1952.

8A. Ricci, G.: Effect of Para-aminobenzoic Acid in Serum Sickness, Acta Vitaminologica **4:**241, 1950.

9. Saslaw, M. S.: Rheumatic Fever—Diagnosis, Prophylaxis, and Therapy, J. A. M. A. **159:**653-656 (Oct. 15) 1955.

10. Good, R. A.; Campbell, B.; and Good, T. A.: Prophylaxis of Allergic Acute Disseminated Encephalomyelitis in Guinea Pigs with Salicylate and PABA, Fed. Proc. **8:**356 (March) 1949.

11. Reppert, E.; Donegan, J; and Hines, L. E.: Ascorbic Acid and Hyaluronidase Hyaluronic Acid Reaction, Proc. Soc. Exper. Biol. & Med. **77:**318-320 (June) 1951.

12. Long, D. A.; Miles, A. A.; and Perry, W. L. M.: Action of Dehydroascorbic Acid and Alloxan on Tuberculin Sensitivity in Guineapigs, Lancet **2:**902-904 (Nov. 17) 1951.

13. Ely, R. S.: Essays on Pediatrics in Honor of Dr. Irvine McQuarrie, Minneapolis, Lancet Publications, Inc., 1955, p. 86. International Symposium on Cortisone, Foreign Letters, Italy, J. A. M. A. **153:**1467 (Dec. 19) 1953.

CORONARY HEART DISEASE IN FORMER FOOTBALL PLAYERS

William C. Pomeroy, M.D., Los Angeles
and
Paul D. White, M.D., Boston

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The health and longevity of athletes has been of considerable interest for 100 years or more and is still a problem of great importance. Not many satisfactory studies have been carried out and published concerning this question, especially as it relates to so-called heart strain and the development of heart disease. Now and then, in the past, some interesting observations have been made, which include a book entitled "University Oars," by Morgan, dated 1873, which discusses the longevity of members of the Oxford and Cambridge crews in the years 1829-1869. Dr. Morgan concluded as follows:

> On the whole the results obtained by the Life Tables, in so far as they bear upon the duration of life of the Cambridge University Oarsmen, must be deemed decidely favourable; the lives of each one of the 32 crews to which they refer extended over 334 instead of 320 years (expected for the male population at large). Hence each individual who rowed is likely to survive the race, on an average, some 42 instead of 40 years.
>
> The lives of the Oxford men are on the whole decidedly better than those of the Cambridge Oars, the former averaging 43.7 years instead of 40 after the race. This is due to the fact that out of the 16 Oxford crews which rowed between 1829 and 1869 only 15 men died within those years, while the deaths among the Cambridge men, who took part in the same races, amount to 24.

Dr. Morgan stated that 11 men died from fever, 7 from consumption, 2 from other forms of chest disease, 6 from accidental causes, 3 from heart affections, 2 from diseases of the brain, 2 from inflammatory attacks, 1 from general paralysis, 1 from calculus, 1 from erysipelas, 1 from Bright's disease, 1 from cancer, and 1 from lupus erythematosus.

Another report of interest was that of Gaines and Hunter, who wrote a paper entitled "Mortality Among Athletes and Other Graduates of Yale Uni-

The health records of a group of 355 men who had distinguished themselves at football in the years 1901 to 1930 inclusive were studied for factors that might predispose a man to coronary heart disease. The cause of death was ascertained in 87 cases and was found to be coronary heart disease in 25. Comparisons were made between former athletes still living without coronary heart disease and former athletes, living or dead, with coronary heart disease, with respect to data that had been recorded during health examinations while they were in college and noted in the years since their graduation. The coronary and noncoronary groups did not differ significantly with respect to body build as recorded in college, but the family histories of the coronary group showed a higher incidence of unfavorable family health and the coronary group gained more weight after leaving college. Little difference was found in this study between heavy smokers and abstainers and between heavy drinkers and abstainers, but it is noted that the groups were small and did not manifest any wide diversity in ways of life. The most interesting finding concerned the amount of exercise taken habitually during the lifetime of these men. Those in the coronary group engaged in less vigorous exercise than did the others, and no individual in this study who maintained a heavy exercise program happened to develop coronary heart disease.

versity" in the *Transactions of the Actuarial Society of America*, in 1905. The author summarized some of the results as follows:

> Combining crew, football, track and baseball and tracing members to the end of 1904, the death rate was nearly 25 per cent lower than among graduates of the Academic Department. Among the 55 deaths there were 12 from tuberculosis of the lungs and 5 from typhoid fever, conditions which would not appear nowadays. A synopsis of the experience of the Yale graduates from 1701 through 1777 indicates a high death rate at ages under 35, nearly three times that in this present generation. It was not until the age group 70 and over that the mortality rates compare with the current ones.

It is well known that coronary heart disease tends to be more common in men of the mesomorphic body type than in those of other (endomorphic and ectomorphic) types. In view of this propensity, it was believed to be desirable to study a group of individuals with this body build, with reference to the possible influence of various environmental factors upon the coronary circulation.

Present Study

It was hoped that Harvard football lettermen of a generation ago would furnish a suitable group for a study of this sort. Questionnaires were sent to all "H" winners in football for Harvard from 1900 to 1930 (except the years 1918 and 1919 when no intercollegiate games of football were played by Harvard because of World War I). Further information was obtained where possible by individual letters to families and to personal physicians. Also, the death certificates for the Commonwealth of Massachusetts were examined for causes of death in cases where no other information was available.

TABLE 1.—*Causes of Death of Eighty-seven Harvard Football Players of a Generation ago*

Causes of Death	Cases	
	No.	%
Coronary heart disease (thrombosis or angina pectoris)*	25	28.8
Malignancies and tumors	11	12.6
Pneumonia	9	10.3
War injuries	9	10.3
Accidents	8	9.2
Suicide	4	4.6
Cerebral hemorrhage*	3	3.4
Typhoid	2	2.3
Generalized arteriosclerosis*	3	3.4
Nephritis	2	2.3
Uremia	2	2.3
Congestive heart failure*	2	2.3
Miscellaneous (1 case each)	7	8.0

* Cardiovascular disease in 33 (37.9%) apparently was due to arteriosclerosis or/and hypertension without congenital, rheumatic, or syphilitic heart disease.

According to the Harvard College alumni records, 424 men won football "H's" in the years 1901 to 1930 inclusive. Of these, 292 were known to be alive, 6 were lost to follow-up, and 126 were known to have been dead as of the date of 1955 on completion of these data. The cause of death was known for 87 of the 126 men. Of the grand total of 424, some information was available concerning 355 persons. It is of interest that, of these, 34 were known to have or to have had definite coronary heart disease.

TABLE 2.—*Causes of Death of Adult White Males in Massachusetts in 1940*

Causes of Death	Deaths			
	No.		%	
Diseases of circulatory system		10,084		42.0
Chronic myocarditis and myocardial degeneration*	3,988		16.6	
Other diseases of myocardium	697		2.9	
Diseases of coronary artery	3,477		14.5	
Angina pectoris	127		0.5	
Chronic affections of valves and endocardium	688		2.9	
Other diseases of circulatory system (including 351 cases of arteriosclerosis)	1,107		4.6	
Suicide		424		1.8
Cancer and other tumors		3,273		13.6
Accidents		1,359		5.7
Cerebral hemorrhage		1,680		7.0
Pneumonia		1,165		4.8
Typhoid		6		0.0
Chronic nephritis (not arteriosclerotic kidney)		863		3.6
Acute nephritis		24		0.1
All other causes†		5,138		21.3
Total		24,026		100.0

* Includes hypertensive heart disease.

† Includes tuberculosis, 1,095 cases; diabetes, 555; cirrhosis of liver, 265; diseases of digestive system, 895; arteriosclerotic kidney, 526; and hypertrophy of the prostate, 266.

Findings

The causes of death in 87 former football players are enumerated in table 1. For purposes of comparison, the causes of death in adult white males in Massachusetts for the year 1940 are listed in table 2. These data were chosen because the median year of death for the group being studied was 1936, and the vital statistics for 1940 were the nearest available for Massachusetts.

A comparison of the percentages of coronary disease in the two groups is difficult because of the vague nature of "chronic myocarditis and myocardial degeneration." Certainly many of these are cases of hypertensive or coronary heart disease. If the cases attributed to cardiovascular disease in each group are compared, it is noted that the former football players have but a slightly lower percentage of death from that cause. It is presumed, of course, that the football players were free of rheumatic and congenital heart lesions at the time of their participation in the sport. They were all carefully examined at that time.

An attempt was made to compare the longevity and mortality of these Harvard football players with that of healthy males of comparable age in the general population or indeed among Harvard graduates who had not played football, but adequate data for any such statistical comparison were lacking. The principal objective of the study, the evaluation of the influence of various factors upon the incidence of coronary heart disease in this group, was approached in two ways.

First, the lettermen with known coronary heart disease were compared with a control group in reference to the factors under study. As a control group, the former football players who are living and have no evidence of coronary heart disease were chosen. The comparison between the coronary group and the control group is made in table 3.

TABLE 3.—*Comparison of Data of Exfootball Players With and Without Coronary Heart Disease*

General Data	Group Living Without Coronary Disease, per Class Grouping						Coronary Group, Both Dead and Living
	1901-1905	1906-1910	1911-1915	1916-1920	1921-1925	1926-1930	
Body build							
Av. height in college, ft.-in.	6-0	5-11½	5-11	6-0	5-11½	5-11½	5-11
Av. weight in college, lb.	173	184	171	187	182	179	182
Av. weight in later life, lb.	175	190	182	199	193	190	200
Marital status, %							
Married	95	86	88	100	98	91	90
Unmarried	5	9	12	0	2	7	3
Divorced	0	5	0	0	0	2	7
Children, av. no.	2.6	2.0	2.4	2.2	2.6	2.3	2.5
Family history of coronary heart disease, %							
None	67	71	62	82	67	57	67
Mild	0	5	0	0	2	6	0
Moderate	33	14	38	18	26	31	13
Severe	0	10	0	0	5	6	20
Habits of exercise, %							
None	0	5	4	8	0	1	18
Minimal	5	32	15	15	17	31	12
Light	19	32	22	31	38	23	52
Moderate	71	22	55	38	37	39	18
Heavy	5	9	4	8	8	6	0
Use of tobacco, %							
None	14	9	26	8	23	25	18
Unspecified amount	10	18	11	8	6	8	10
Minimal	14	14	0	0	3	3	0
Moderate	48	41	33	46	38	34	28
Heavy	14	18	30	38	29	30	44
Use of alcohol, %							
None	0	18	22	8	14	9	11
Unspecified amount	5	18	7	8	5	7	5
Minimal	29	23	4	8	8	11	21
Moderate	57	41	56	76	67	65	52
Heavy	9	0	11	0	6	8	11
Caloric intake, %							
Moderate	100	86	100	67	90	96	77
Heavy	0	14	0	33	10	4	23
Fat intake, %							
Light	20	14	17	0	24	8	0
Moderate	80	72	83	100	59	84	75
Heavy	0	14	0	0	17	8	25
Cholesterol intake, %							
Light	20	0	17	33	10	4	0
Moderate	80	57	50	67	59	64	83
Heavy	0	43	33	0	31	32	17

It will be noted that the control group is broken down into groups of five graduating classes (1901 to 1905, 1906 to 1910, and so on). This breakdown was made so that it would be possible to note any changing trends during the 30 years covered by this study.

If table 3 is examined, it will be seen that the body build in college of the coronary group did not differ significantly from that of the control group. The coronary group did, on the whole, gain more weight than the control group. There was a definite difference here, though not of great magnitude. The family status of the coronary group does not differ markedly from that of the control group except that there were more divorces in the group with coronary heart disease. This may or may not represent a factor of stress. With reference to a family history of coronary heart disease, the ex-athletes who eventually developed coronary heart disease had a definitely higher occurrence of "unfavourable family health." This meant, in most cases, that both parents had had coronary heart disease.

TABLE 4.—*Comparison of Extremes in Data on Weight Gain, Exercise, and Use of Tobacco and Alcohol in Exfootball Players*

Current Data	Classes, No. of Persons						Total
	1901-1905	1906-1910	1911-1915	1916-1920	1921-1925	1926-1930	
Marked weight gain (40 lb. or more)							
Living and well	0	2	1	2	6	8	19
Coronary heart disease	2	2	2	0	0	1	7
Other significant disease	4	0	3	0	0	5	12
Little or no weight gain (5 lb. or less)							
Living and well	3	1	1	2	5	8	20
Coronary heart disease	1	3	0	0	0	0	4
Other significant disease	6	2	5	1	2	5	21
Heavy exercise							
Living and well	0	0	1	1	3	4	9
Coronary heart disease	0	0	0	0	0	0	0
Other significant disease	1	2	2	0	2	1	8
Little or no exercise							
Living and well	1	5	2	3	10	21	42
Coronary heart disease	2	1	1	0	0	2	6
Other significant disease	1	4	3	0	1	7	16
Heavy smoker							
Living and well	2	4	4	5	15	20	50
Coronary heart disease	0	1	3	0	2	0	6
Other significant disease	1	2	4	2	4	7	20
Nonsmoker							
Living and well	3	3	3	1	10	9	29
Coronary heart disease	0	1	2	0	0	1	4
Other significant disease	2	0	4	0	5	12	23
Heavy drinker							
Living and well	1	0	0	0	2	4	7
Coronary heart disease	0	1	0	0	1	0	2
Other significant disease	1	0	3	0	2	3	9
Nondrinker							
Living and well	0	3	2	1	5	5	16
Coronary heart disease	1	0	1	0	0	0	2
Other significant disease	0	2	4	0	2	3	11

The most interesting finding of the entire study concerned the amount of exercise. As can be seen from table 4, the men in the coronary heart disease group engaged in less vigorous exercise than did those without heart disease. The objection

might be raised that these figures are from the period after the onset of heart disease, and thus represent a curtailing of normal activity. This is not the case, since the lifelong habits of exercise were investigated. This is an important finding.

With reference to the use of tobacco, there were a few more heavy smokers than nonsmokers in the coronary heart disease group. This is not of statistical significance. The use of alcohol was about the same in both groups.

With reference to diet, it is difficult to draw definite conclusions because of the probable inaccuracies of estimation by those filling out the questionnaires. There seems to be little difference with reference to caloric intake. The coronary group generally ate more fat than did the control group, though, as noted above, all of the figures relating to diet are open to question.

The second method of investigating the effect of the various factors being studied was the comparison of the extremes in each instance. These data are listed in table 4 by number of cases. If the "H" men who gained 40 lb. or more are compared with those who had little or no weight gain, it can be seen that there was an increased risk of developing coronary heart disease in those with the marked weight gain. With reference to exercise, although there were relatively few exathletes who continued a strenuous program of physical activity, it appeared that a heavy exercise program tended to protect against coronary disease. On the other hand there seemed to be little difference between heavy smokers and abstainers and between heavy drinkers and abstainers with reference to the development of coronary heart disease, although there were but limited numbers in both of these groups; the average Harvard graduate used tobacco and alcohol in a moderate degree.

Summary and Conclusions

A questionnaire study has been made of the prevalence of coronary heart disease in mesomorphic exathletes and of the influence of various environmental factors upon its development. An attempt was made to follow up 424 Harvard College students who won their football H's in the years 1901-1930 inclusive. Of these, in 1955, 126 were known to have died and 292 to be alive; 6 could not be traced. The cause of death was known in 87 of the 126. Among these, coronary heart disease was responsible for 25 deaths, or 29%. Cerebral hemorrhage, generalized arteriosclerosis, and congestive heart failure accounted for 8 more cases, making the total 33 cardiovascular deaths, or 38%. Cancer apparently caused 11 deaths, or 13%; pneumonia and war injuries 9 deaths each, or 10%; accidents 8 deaths, or 9%; suicide 4 deaths, or 5%; typhoid 2 deaths; and the balance miscellaneous.

An attempt was made to compare these figures with those of the white male population of the same age group in Massachusetts in whom cardiovascular deaths amounted to 44%, cancer 13%, accidents 7%; and pneumonia 5%. The cardiovascular deaths included an uncertain number of cases of coronary heart disease labeled as such in 13% and probably included under the designation of chronic myocarditis or degeneration, which was recorded as 16%. The mortality of these football players as compared with healthy males of the same age in the general population could not be determined because of the inadequacy of data.

The following relationships in the group of football players were compared for persons whose history showed the presence of coronary heart disease and for those without coronary heart disease: body build, weight gain, personal family status, family history, habits of exercise, use of alcohol and tobacco, and diet.

Body build did not differ significantly, but there was more weight gain in the coronary group than in the other. The family status was not significantly different except that there were more divorces in the coronary group. There was a higher percentage of family history of coronary heart disease in the coronary group than in the control group. One of the most significant findings in the study was the apparent protection afforded by the continuation of a program of heavy exercise. Those who maintained even moderate habits of exercise were less prone to coronary heart disease, and no individual in this study who maintained a heavy exercise program happened to develop coronary heart disease. There was a higher percentage of heavy smokers in the coronary group, but the difference was not marked. Alcohol appeared to have little influence on the development of coronary heart disease. The lack of detailed and accurate information about the dietary habits prevented any satisfactory conclusions in that area.

The chief defect revealed in a study of this sort lies in the uniformity of the ways of life of most Harvard and other college graduates and, therefore, in the difficulty of comparing extremes because of the inadequate numbers represented therein. A study of racial groups, of which certain members, either in the country of their origin or when transplanted elsewhere, live very differently from others of the same race, should prove more instructive.

264 Beacon St. (Dr. White).

MULTIPLE CAUSES OF IRON DEFICIENCY IN INFANTS

Calvin W. Woodruff, Nashville, Tenn.

The possible causes of hypochromic anemia were sought in a study of 272 infants whose blood had been found to contain less than 9 Gm. of hemoglobin per 100 cc. The most common factor was prematurity or a birth weight of less than 3,000 Gm. Prematurity was present in 80% of the patients with a hemoglobin concentration of less than 5 Gm. per 100 cc. The incidence of severe hypochromic anemia in infants weighing more than 4,000 Gm. is extremely low. A first child was less liable to become anemic than were later siblings; single children were less liable than twins; and girls less liable than boys. Dietary information was incomplete, but the most frequent dietary pattern, before treatment, was found to have been two quarts of milk daily, supplemented with mashed potatoes, dried beans, crackers, or bread. The evidence showed, however, that deficient iron intake was not the sole cause of severe hypochromic anemias. Prevention therefore depends largely on the recognition of susceptible infants in the population. These should be watched carefully and treated prophylactically with adequate doses of medicinal iron.

Despite an increasing body of knowledge concerning iron metabolism, the incidence of hypochromic anemia approaches 30% of infants in the second year of life in at least one large pediatric clinic.[1] The continued occurrence of a preventable disease in such a large number of infants is a shocking public health problem. The prevention of iron deficiency and its associated hypochromic anemia depends on sound knowledge concerning its etiology.

Present knowledge of iron metabolism in infants [2] suggests four possible mechanisms for the development of iron deficiency. The first is deficient stores of iron at birth. The amount of iron in the circulating hemoglobin and in the tissues of the newborn infant can be reduced because of maternal deficiency or by blood loss during the perinatal period. A second possibility is the relative growth rate. Small infants, especially premature infants, tend to grow faster in relation to their birth weight. The demands of the body for iron are increased. The relatively rapid expansion of the hemoglobin mass is a major component of the iron needs. A third possibility is a deficient intake of iron by the infant. Iron deficiency anemia has been known as "nutritional anemia" and "milk anemia" because of the recognized importance of the iron intake in its development. Defects in absorption of iron should be considered as conditioned iron lack in this category. A fourth possible mechanism is blood loss; this is the most common mechanism of development of iron deficiency in adults. Chronic blood loss may be an important cause of iron deficiency in infants harboring hookworm and other parasites. Its frequency in their absence is unknown. An attempt to define the relative importance of these factors in the pathogenesis of hypochromic anemia in infancy is the subject of the present study.

Description of Sample

A survey of three years of experience with hypochromic anemia in this clinic has been made as a background for a broader program for investigation of iron metabolism in infants. All the infants in this study had a hemoglobin concentration of less than 9 Gm. per 100 cc. and either a mean corpuscular hemoglobin concentration (MCHC) of less than 30% or a definite response to iron therapy. These criteria indicate anemia of at least moderate severity and avoid confusion with physiological variations in hemoglobin concentration. The data analyzed in this report were obtained from the hospital records and were limited to those items considered to be equally valid for all of the cases studied. These patients were seen in either the outpatient department or the wards of Vanderbilt University Hospital between Jan. 1, 1954, and Dec. 31, 1956. Many of these infants were admitted for the treatment of acute illnesses. While this group of patients is more characteristic of the experience of an active pediatric service than of the population at large, it is felt to be a representative group of anemic infants.

Results

A total of 272 cases of hypochromic anemia was seen during this three-year period. The yearly frequency was related to the total number of visits to the outpatient department and hospital of children under 16 years of age (excluding newborn infants and well babies). In 1954, in a total of 9,833 visits, 69 cases (0.70%) were determined; in 1955, 78 (0.76%) in 10,223 visits; and in 1956, 125 (1.13%) in 11,057 visits. The more frequent oc-

From the Department of Pediatrics, Vanderbilt University School of Medicine. Dr. Woodruff is a Markle scholar in medical science.

currence in 1956 represents my interest in collecting cases. This has resulted in the inclusion of many which were diagnosed and treated without being recorded by means of a formal diagnosis. There is every reason to suspect that a similar incidence occurred in the two previous years. No seasonal trend could be identified.

The age distribution of the cases is shown in table 1. Only one instance of hypochromic anemia was diagnosed in a patient more than 5 years old.

TABLE 1.—*Age Distribution of Patients with Anemia*

Age, Mo.	Cases, No. Total	In Premature Infants
6- 6	6	4
7- 9	50	21
10-12	70	20
13-15	44	15
16-18	40	12
19-21	24	6
22-24	10	1
25-27	12	...
28-30	4	...
31-60	12	...
Total	272	79

His anemia was iatrogenic and developed during the study and treatment of a complex metabolic problem. This case has been omitted from the compilation. All but 12 cases occurred in patients under the age of 30 months. In the remainder, the ages were rather evenly distributed between 30 and 60 months. Anemia was recognized in the premature infants before the age of 24 months.

The data on race and sex are presented in table 2. The population of our outpatient department is approximately 40% Negro. The disease incidence of 36% in Negro infants does not suggest any racial differences. Anemia was more frequent in male

TABLE 2.—*Sex Ratio of Patients with Hypochromic Anemia*

Birth	Race	Male No.	Found, %	Expected*, %	Chi-square	p
Term	White	119	53.8	51.9	0.162	Not significant
	Negro	56	71.3	51.5	8.19	0.004
Premature	White	44	63.6	46.2	4.74	0.03
	Negro	35	71.4	42.6	10.78	0.001
Total	White	174	58.0	51.5	2.99	Not significant
	Negro	98	71.5	50.4	16.49	0.001

* Duffield and others: Child 5:123, 1940.

infants than in females. With the exception of the full-term white infants this difference was statistically significant in the subgroups presented in table 2.

The distribution of 254 patients with anemia by birth weight is compared in figure 1 with the birth weight distribution of total live births in Tennessee in 1954. Sex and race differences in birth weight have been omitted from the figure since they were small when compared to the deviation of this group of patients from the population as a whole. The total incidence of prematurity (including twins) was 31.1%, subdivided as follows: white males, 30.4%; Negro males, 38.5%; total males, 33.7%; white females, 22.5%; Negro females, 38.5%; total females, 26.8%; total white births, 27%; and total Negro births, 38.5%.

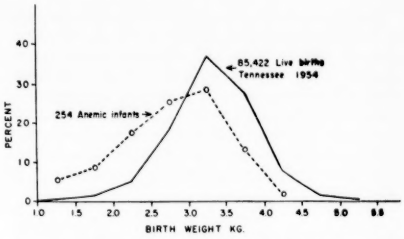


Fig. 1.—Birth weight distribution of 254 patients with hypochromic anemia of both sexes and both races compared with that of total live births in Tennessee in 1954.

The birth order of these patients is shown in figure 2 and is compared with similar data for Tennessee for 1954. The data for white and Negro infants are presented separately. The frequency of anemia in the white infants increased as birth order increased, reaching a peak with the fourth-born infant. A rather different pattern was seen among the Negro infants, with a peak incidence for second-born infants. It is felt that the Negro patients in this group are not a representative sample, and interpretation of this difference will not be attempted.

The weight of the infant at the time his anemia was recognized is plotted against age in figure 3. The 10th, 50th, and 90th percentiles for males are

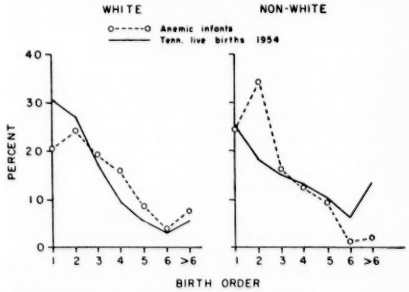


Fig. 2.—Birth order of 174 white and 98 Negro infants with hypochromic anemia compared with that of total live births in Tennessee in 1954.

the frame of reference. No race or sex differences are apparent. Premature infants are plotted separately. With five exceptions, the infants under 30 months of age fell below the 10th percentile. Eighty per cent of the premature infants and 37%

of the full-term infants fell below the 90th percentile. The weight of the infants over 30 months old have not been included in the figure but have a similar distribution. As a group, these infants appear to be underweight, but not to a degree incommensurate with their small size at birth.

The distribution of hemoglobin concentrations of the sample is given in figure 4. In 41 (15%) of the infants, the hemoglobin was less than 5 Gm. per 100 cc. One infant had a hemoglobin level of 1 Gm. per 100 cc. Sixty per cent of these severely anemic infants weighed less than 2,500 Gm. (5.5 lb.) at birth. No correlation between race, sex, or age and hemoglobin concentration was found.

Twenty-six of the infants in the whole series were twins. Both members of nine pairs were anemic; only one member was anemic in eight instances. Twenty of the twins were premature on the basis of birth weight. In table 3 the incidence of twins is given with the various birth weights, sex, and race groups. In each instance it is higher than would have been expected.

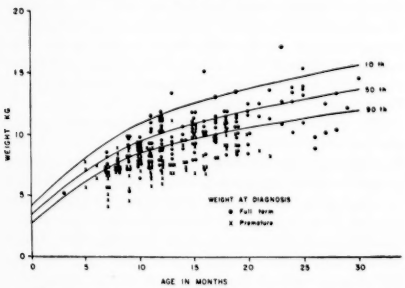


Fig. 3.—Weights of infants with hypochromic anemia occurring under the age of 30 months compared with normal values for white males.

In 25 cases a history of maternal anemia or blood loss during pregnancy was obtained. In only four cases could this information be quantitated. In two of these the maternal hemoglobin concentration was 7 and 8.5 Gm. per 100 cc. at the time of delivery. In two other cases transfusions of the mother had been required. These four infants could not be differentiated from the rest of the group on the basis of any of the parameters studied.

A history of blood loss was obtained in four cases. Two infants had melena and two epistaxis. There were four cases of scurvy. Dysproteinemia was suspected in four infants who had serum albumin concentrations below 2.5 Gm. per 100 cc.

The dietary histories of all the patients were reviewed. The material was not accurate enough for detailed analysis. The most frequent dietary pattern consisted of two quarts of milk daily, usually from a bottle. Those infants receiving any supplement had mashed potatoes, dried beans, crackers, or bread. The diets were characterized by the absence of the iron-fortified cereals, vegetables, eggs, fruits, and meat. A few of the premature infants appeared to be ingesting diets that were adequate. With very few exceptions, prophylactic iron therapy had not been given.

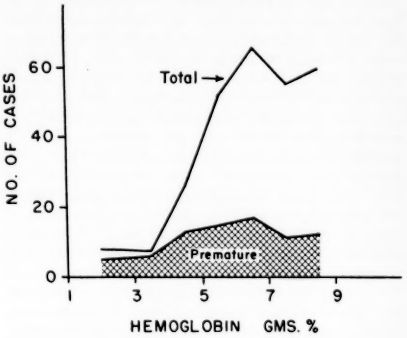


Fig. 4.—Hemoglobin concentration of 272 patients, with separate presentation of premature infants.

There were three deaths among these patients. All occurred within a few hours after admission. One infant had epiglottitis due to Hemophilus influenzae. The other two had pneumonia with cardiac decompensation. In the last two cases it would seem likely that the infants might have survived their infections had they not been anemic.

Comment

The probable causes of iron deficiency in this series of infants will be discussed under the four mechanisms suggested in the introduction, i. e., iron supplies at birth, relative growth rate, available dietary iron, and iron loss.

TABLE 3.—*Number of Twins in Present Series Subdivided by Race, Sex, and Prematurity Compared with Expected Incidence**

Birth	Race		Twins, No.	
			Found	Expected
Full-Term	White	M	1	0.6
		F	4	0.5
	Negro	M	1	0.4
		F	0	0.1
	Total		6	1.6
Premature	White	M	7	4.3
		F	3	2.7
	Negro	M	8	3.7
		F	2	0.6
	Total		20	11.8

* Duffield and others: Child 5:123, 1940.

Iron Supplies at Birth.—The total body iron at birth may be considered in terms of iron concentration (in milligrams per kilogram of body weight),

so that infants of varying birth weights may be compared directly. There is experimental justification for this approach in the data of Widdowson and Spray,[3] who found that the iron concentration during fetal life was relatively constant, with an average value of 75 mg. per kilogram of body weight. The extent of variation from this mean value is not accurately known. Calculations of the iron concentration at birth, based on average values for blood volume and hemoglobin concentration with the addition of an assumed value for tissue stores, are probably less reliable than the actual analyses of Widdowson and Spray. Josephs [4] has recently reviewed this subject and arrived at a normal value of 80 mg. per kilogram of body weight. Variations in such calculations have been discussed by Sturgeon,[2b] who suggested that the total iron level at birth could vary from 129 to 300 mg. in normal, full-term infants. These calculations cover a range of 43 to 75 mg. per kilogram of body weight. The assumption that the iron concentration at birth is normal in infants later developing hypochromic anemia does not rest on any direct evidence. Several recent reports emphasize the variability in iron stores at birth. Kaldor [5] has reported that the iron concentration in the fetal liver is lower in smaller infants. Sisson and Lund [6] have calculated the hemoglobin mass from the plasma volume at 4 or 5 days of age in 25 infants born to anemic mothers and have found a reduction of 3.5 Gm. of hemoglobin per kilogram of body weight, which equals 11.7 mg. per kilogram of iron, or about 19% of the total body concentration of iron. Such differences in hemoglobin mass are large enough to be of critical importance in the infant's iron economy and can exist without the presence of "anemia," as measured by hemoglobin concentration alone. At the present time, it is believed that the circulating hemoglobin mass constitutes the largest iron "store" in the newborn infant.[2a]

Reduction in the iron concentration at birth may occur through either maternal or fetal factors. The maternal factors have been discussed elsewhere.[7] In the present series they are represented by an increased frequency of incidence of anemia in a high birth order and by the four mothers who were anemic at term. In this sample, few cases could be ascribed to maternal factors alone.

The recognized fetal factors operating to reduce the iron concentration at birth are limited to hemorrhage, especially that from the placental circulation. An increasing number of case reports of fetal hemorrhage into the maternal circulation have recently appeared. Fetal exsanguination and shock from acute blood loss in the neonatal period has also received attention. An incidence of 7 cases in 7,400 deliveries was found in this hospital. These cases have threatened the existence of the infants. The number of hemorrhages of similar nature but of lesser degree that have gone unrecognized is unknown. Blood loss in the perinatal period may be a cause of iron deficiency in later infancy.

Evaluation of the possible role of so-called placental transfusion in determining the iron supplies at birth will not be possible until more quantitative data are available.

The special circumstance of multiple births needs to be considered under fetal factors. The frequent occurrence of hypochromic anemia in twins has been recognized for many years. Since twinning occurs with a greater frequency than might be expected in all the race, sex, and birth weight groups in this study, there must be an explanation other than the obvious one of low birth weight. The frequency of abnormal placental circulation is more common in multiple than in single births, especially in single-ovum twins. This is accompanied by an increased incidence of acute blood loss and shock in the neonatal period. The transfusion of one twin by the other can and does occur. Such transfusions could well explain the relatively frequent occurrence of hypochromic anemia in only one of twins when both had similar growth rates and diets. Six twins in this series may well come under this category. Finally, the obvious fact that the twins must divide the available transplacental iron remains as a definite possibility.

The preponderance of male infants in this group, particularly among those born prematurely, is surprising since no reference to an altered sex ratio in patients with iron deficiency has been found. Among premature infants who survive the neonatal period, males constitute the minority group. If the greater mortality among males after the first month of life had been considered in this analysis, the differences would become even more significant statistically. Male infants are less mature than female infants of the same weight as measured by epiphysial ossification [8] and by neonatal mortality.[9] During the course of an investigation of the hemoglobin concentration of infants born to a group of mothers whose nutritional status had been investigated, it was noted that the hemoglobin concentration of male infants was significantly less at the age of 5 to 7 weeks than that of the female infants. Studies of the serum iron concentration in children aged 3-14 years [10] showed lower values among males than among females, a reversal of the situation found in adults. The growth of male infants during the first year of life is greater than that of female infants. On calculating hemoglobin growth on the basis of published values for normal growth and hemoglobin concentration, Drabkin [11] demonstrated increments of 40 Gm. for males and 30 Gm. for females during the first year of life. His calculations indicate that the iron needs of males are greater than those of females during the first year of life. These observations suggest the possibility that sex differences in iron metabolism may occur

in infancy as well as in adults. Rachitic tetany and keratomalacia are other nutritional diseases which are known to occur more frequently in males. The preponderance of males in this group of anemic infants is probably related in some way to their relative immaturity as well as to the greater growth rate of males over females.

Relative Growth Rate.—Since the growth rate for large and small infants, as expressed in terms of daily weight gain, remains within relatively narrow limits for both males and females, the main determinant of the relative growth rate is the birth weight itself. The role of low birth weight as a predisposing factor in the development of hypochromic anemia has been documented by Mackay,[12] Davidson and Fullerton,[13] and many others. Despite rather widespread recognition of the fact that premature infants are particularly prone to develop iron deficiency, they still constitute the largest single group of anemic infants from an epidemiologic standpoint. The increased incidence of iron deficiency found in infants weighing 3,000 Gm. (6.5 lb.) or less includes several infants not considered to be immature by more general standards. The most striking observation is the extremely low incidence of severe hypochromic anemia in infants weighing more than 4,000 Gm. (9 lb.). These infants are subjected to the same environmental and dietary factors as the other infants in this series. It must be concluded that their iron needs are less because of a relatively slower growth rate and that their initial total iron supply is greater due to their greater tissue mass.

Dietary Iron.—The dietary iron available could not be estimated from the histories and is unknown in these patients. The fact that they all developed hypochromic anemia is evidence that their iron retention was inadequate. Iron intake considerably in excess of the recommended dietary allowances can easily be achieved.[14] Calculations of the iron needs of infants during the first year of life [2b] suggest that, in some cases, these needs cannot be supplied by ordinary diets. There is little question concerning the fact that diets consisting largely of milk are frequently associated with the development of hypochromic anemia after the age of 6 months.

Iron Loss.—No studies of iron excretion in infants comparable to those done in adults [15] have been carried out. There is no reason to believe that infants conserve iron less well than adults. Occasional cases of hypochromic anemia after blood loss due to trauma or disease do occur. The role of iron excretion in infants as a cause of iron deficiency needs quantitative reevaluation.

Summary and Conclusions

An attempt has been made to determine whether the composition of a group of anemic infants differs from that of the population from which they are drawn. The most significant predisposing factors found were low birth weight, high birth order, twinning, and masculinity. Similar findings were recently reported by Guest and Brown.[16] The poor diets eaten by these infants are similar to those of a much larger number of infants who did not develop anemia of the same degree of severity. Consequently, severe hypochromic anemia in infancy does not occur solely as the result of a deficient iron intake.

Prematurity or a birth weight of less than 3,000 Gm. (6.5 lb.) is the most common predisposing factor. Prematurity was present in 80% of the patients with a hemoglobin concentration of less than 5 Gm. per 100 cc. Reduction of the iron supplies at birth may be due to maternal iron deficiency or fetal blood loss. Unrecognized instances of fetal blood loss may compromise the infant's iron economy without jeopardizing his life. Perinatal hemorrhage may also be an explanation for the high incidence of hypochromic anemia in twins. The more frequent occurrence of hypochromic anemia in male infants is a reflection of their relative immaturity and increased growth rate.

The prevention of hypochromic anemia depends largely on the recognition of the susceptible infants in the population. This group should be given adequate doses of medicinal iron prophylactically and should be carefully watched for the development of anemia.

Vanderbilt Hospital, 21st and Edgehill Streets (5).

This study was supported by grants from Mead Johnson & Company, Evansville, Ind.

Dr. Margaret Martin did the statistical analysis of the data, and Mrs. S. H. Pierce Jr. and Mrs. Willard Faulkner assisted with the compilations.

References

1. Lahey, M. E.: Iron and Copper in Infant Nutrition, Am. J. Clin. Nutrition **5**:516-526 (Sept.-Oct.) 1957.

2. (*a*) Josephs, H. W.: Iron Metabolism and Hypochromic Anemia of Infancy, Medicine **32**:125-213 (May) 1953. (*b*) Sturgeon, P.: Iron Metabolism: Review with Special Consideration of Iron Requirements During Normal Infancy, Pediatrics **18**:267-298 (Aug.) 1956.

3. Widdowson, E. M., and Spray, C. M.: Chemical Development in Utero, Arch. Dis. Childhood **26**:205-214 (June) 1951.

4. Josephs, H. W.: Hypochromic Microcytic Anemia of Infancy: Iron Depletion as Factor, Pediatrics **18**:959-978 (Dec.) 1956.

5. Kaldor, I.: Storage Iron in Fetus, Australasian Ann. Med. **4**:277-278 (Nov.) 1955.

6. Sisson, T. R. C., and Lund, C. J.: Influence of Maternal Iron Deficiency on Newborn, Am. J. Clin. Nutrition, to be published.

7. Woodruff, C. W.: Maternal Factors in Hypochromic Anemia of Infancy, report to the Council on Foods and Nutrition, J. A. M. A. **162**:659 (Oct. 13) 1956.

8. Dunham, E. E.; Jenss, R. M.; and Christie, A.: Consideration of Race and Sex in Relation to Growth and Development of Infants, J. Pediat. **14**:156-160 (Feb.) 1939.

9. Shapiro, S.: Influence of Birth Weight, Sex, and Plurality on Neonatal Loss in United States, Am. J. Pub. Health **44**:1142-1153 (Sept.) 1954.

10. Hagberg, B.: Iron Binding Capacity of Serum in Infants and Children, Acta Pædiat. (supp. 93) **42**:1-80, 1953.

Vahlquist, B. C.: Das Serumeisen. Eine pädiatrisch-klinische und experimentelle Studie, Acta Pædiat. (supp. 5) **28**:1-374, 1-68, 1941.

11. Drabkin, D. L.: Metabolism of Hemin Chromoproteins, Physiol. Rev. **31**:345-431 (Oct.) 1951.

12. Mackay, H. M. M.: Factors Causing Variation in Hemoglobin Level with Age in First Year of Life, Arch. Dis. Childhood **8**:251-264 (Aug.) 1933.

13. Davidson, L. S. P., and Fullerton, H. W.: Chronic Nutritional Hypochromic Anæmia, Edinburgh M. J. **45**:1-23 (Jan.) 1938.

14. Beal, V. A.: Nutritional Intake of Children: II. Calcium, Phosphorus and Iron, J. Nutrition **53**:499-510 (Aug.) 1954.

15. Dubach, R.; Moore, C. V.; and Callender, S. T.: Studies in Iron Transportation and Metabolism: IX. Excretion of Iron as Measured by Isotopic Techniques, J. Lab. & Clin. Med. **45**:599-615 (April) 1955.

16. Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of Blood in Infancy and Childhood: III. Factors in Variability, Statistical Studies, A. M. A. J. Dis. Child. **93**:486-509 (May) 1957.

URINARY CALCULI

EXCRETION STUDIES AFTER ORAL ADMINISTRATION OF ACETYLSALICYLIC ACID AND GLUCURONOLACTONE

Frank C. Hamm, M.D., Sidney R. Weinberg, M.D.
David Karansky, M.D., Leo Kesner, B.S.
and
Philip Lewis, B.S., Brooklyn, N. Y.

Determinations of the factors involved in the solubility of calcium were made before and after the administration of acetylsalicylic acid and glucuronolactone in normal persons and in patients who had formed stones. The pH values of urine did not change after the drugs were administered. There was no alteration of the surface tension after the administration of acetylsalicylic acid or glucuronolactone in normal individuals or those with stones. The administration of acetylsalicylic acid or glucuronolactone did not increase either the total excretion per day or the concentration of calcium and phosphorus per milliliter beyond the range of values that existed before the drugs were given. The concentration of organic acids, such as citrates or glucuronides, in urine also have a direct bearing on the solubility product of calcium phosphate. The administration of glucuronolactone and acetylsalicylic acid in all instances raised the concentration of the glucuronides in urine, but the equilibration experiments as described did not show any direct solvent action of the glucuronides on the calcium in urine at pH 6 and the physiological concentration used.

Though the etiology and pathogenesis of primary calcium urinary stones have not been determined, one possible etiological factor, that of quantitative increase of calcium in urine, appears implicated in many instances. However, the amount of calcium that urine can maintain in solution without precipitation, or its solubility, is unknown.[1] It is generally believed that urine is supersaturated with calcium, as determined by equilibration experiments in which urine of known calcium content is agitated with excess calcium phosphate. If precipitation occurs, calcium goes out of solution, and a supersaturated state is shown to exist; if some of the excess calcium phosphate goes into solution, then a state of undersaturation probably preexisted. Flochs [2] and Andrews [3] found supersaturation common in the urines of stone-forming patients. Hyperexcretion of calcium is thought to be an etiological factor in the increased incidence of urinary stones in recumbency and hyperparathyroidism.

The physical state of calcium in urine has a direct bearing on its solubility. It can be assumed that calcium in urine is present either as free ions in equilibrium with calcium phosphate or held in unionized organic compounds by union with citrates or glucuronides.[4] It is obvious that the greater the amount of calcium held in organic union, the fewer free calcium ions will be available for precipitation and presumably for calculus formation.

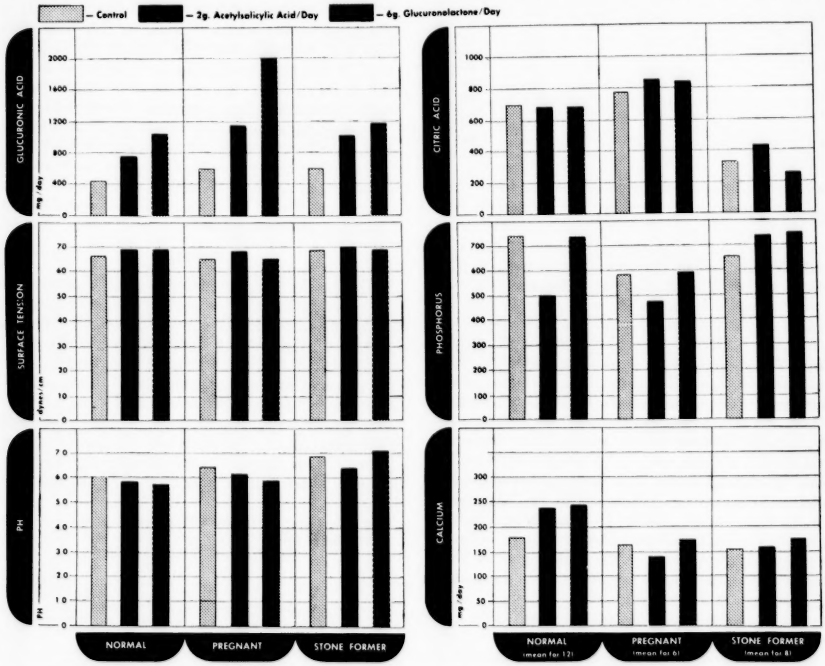
From the Department of Surgery, Division of Urology, State University of New York Downstate Medical Center.

Read before the Forum of Fundamental Surgical Problems at the Clinical Congress of the American College of Surgeons, October, 1957, Atlantic City, N. J.

With this in mind, Prien and Walker [5] have drawn attention to the possible solubilizing effects of glucuronides on calcium in urine. They have

recommended the administration of acetylsalicylic acid or salicylamide as drugs that can enhance the formation of calcium-glucuronide, a chelated organic union similar to the calcium-citrate complex, and thus prevent the formation and growth of calculi in the urinary tract. This premise is based on experiments by Neuberg and Grauer [6] who showed that the presence of menthol glucuronide in an in vitro solution of calcium chloride and monobasic sodium phosphate can prevent calcium precipitation. However, a 0.139 solution of menthol glucuronide containing 46 Gm. per liter was used, a concentration that cannot be obtained in physiologic solutions. Cessi's [7] work, which followed the studies of Neuberg and Grauer, may also have bearing on the solubility of calcium salts in urine. Cessi's experiments were done with isolated liver slices and demonstrated absorption of tagged tribasic calcium phosphate from physiologic saline solution by the liver slices through the action of the glucuronides. Neutral or slightly alkaline tissue pH is necessary for the formation of an adequate amount of the enzyme glucuronidase which acts as a catalyst for the reaction.

If an analogy can be drawn between the reactions in the liver slices and those in the kidney, then the administration of acetylsalicylic acid and glucuronolactone, which leads to an increased amount of glucuronides in the urine and presumably in the tissues, might alter the concentration or the state of calcium in plasma and perhaps aid in the clearance of calcium. If so, perhaps subjects to whom acetylsalicylic acid, salicylamide, or glucuronolactone was administered might have different amounts of calcium in their urine than before the administration of these drugs. To test this theory, determinations of the factors involved in the solubility of calcium were done before and after the administration of acetylsalicylic acid and glucuronolactone both in normal individuals and in those patients who had formed stones. The determinations were performed in individuals of varying race, age, and sex and in pregnant women. It was hoped



Quantitative evaluation of urinary excretion factors concerned with solubility of calcium in urine of 26 persons.

that a range of normal variation for comparison would further delineate these values in stone-forming patients.

Methods

Twenty-six patients, of whom 12 were normal individuals, 6 were pregnant women, and 8 were stone-formers, were studied as follows: Each subject had 24-hour urine specimens collected as controls on the first two days of the experiments. On the third, fourth, and fifth days, each experimentee was given 6 Gm. of glucuronolactone per day and had 24-hour urine specimens collected on the fourth and fifth days. On the sixth, seventh, and eighth days each individual was given 2 Gm. of acetylsalicylic acid per day and had 24-hour urine specimens collected on the seventh and eighth days. The subjects were on unrestricted diets. Surface tension, specific gravity, and pH determinations were done on uncentrifuged urine. Determinations of the calcium, phosphorus, citric acid, and glucuronide content of the urines were done on centrifuged aliquot samples obtained from the 24-hour specimen, which had been preserved with toluene. It had been determined in our laboratory by 11 experiments (table 1) that in uninfected urine the calcium and phosphorus content of both uncentrifuged urine and urine centrifuged for five minutes at 1,500 rpm is approximately the same, suggesting that any calcium phosphate not in solution remains in suspension in urine and does not precipitate at room temperature after centrifuging.

Specific gravity was measured by a urinometer. Surface tension was measured by means of a Revici urotensiometer,[8] a rapid method useful for comparing urines of various groups, that is, from normal individuals and stone-formers. The pH was read on a Beckman pH meter. The calcium level was determined by means of the flame photometer attachment of the Beckman DU spectrophotometer.[9] The phosphorus level was determined by the method of Fiske and Subba Row.[10] The citrate levels were determined by the method of Pucher,[11] and the glucuronic acid level was determined by the Tollens napthoresorcinol test as modified by Fishman.[12]

TABLE 1.—*Calcium and Phosphorus Levels, in Milligrams per Liter, in Centrifuged and Uncentrifuged Twenty-four-Hour Urine Specimens*

Sample No.	Centrifuged		Uncentrifuged	
	Calcium	Phosphorus	Calcium	Phosphorus
1	156.0	1,000	154.8	1,000
2	41.4	630	40.4	630
3	72.2	460	74.6	450
4	24.6	210	25.8	200
5	52.8	635	52.8	642
6	30.2	200	30.6	202
7	32.4	200	32.4	190
8	20.2	390	20.0	460
9	59.4	360	59.4	360
10	5.4	570	5.4	590
11	21.4	340	20.4	310

In addition, equilibration experiments were done to determine whether any alteration of calcium solubility takes place after the administration of the drugs because of any possible increased content of citrate or glucuronide in the urine. In these experiments 50 cc. of urine of known calcium content was equilibrated with calcium phosphate for two hours, after which a similar sample was equilibrated with the same amount of calcium phosphate plus a 0.003 M (1.7 Gm. per liter) solution of menthol glucuronide to determine if the drug per se could alter the solubility of calcium in urine. These experiments were conducted at the pH of the urine as formed. The concentration of 1.7 Gm. per liter of glucuronide was decided upon, as this concentration was approximately the highest physiological level of the glucuronides in urine as found in over 200 determinations in our experiments previously cited. Vermeulen has presented similar findings.[13]

In a similar series of experiments, 250 cc. of urine was equilibrated with calcium phosphate plus 0.1 Gm. of acetylsalicylic acid. This experiment was decided upon, as 20% of acetylsalicylic acid is excreted unchanged in urine while the remainder is altered to glucuronic acid.[14]

Results

The results were tabulated for each patient, and the individual results were then averaged (see figure). Our conclusions are as follows: 1. The pH values of urine do not change after the drugs are administered. 2. Surface tension is an expression of the physical state of urine as related to the colloid-crystalloid balance. Differences in the surface tensions of urines obtained from persons who form stones and those of normal patients have been reported.[15] Our studies do not indicate any such difference. There was no alteration of the surface tension after the administration of acetylsalicylic acid or glucuronolactone in the three classes of subjects tested. 3. The concentration of free calcium ions multiplied by the concentration of phosphate ions determines the critical level in urine for precipitation of calcium phosphate. Our results indicate that the administration of acetylsalicylic acid or glucuronolactone did not increase either the total excre-

TABLE 2.—*Effect of Calcium Phosphate and 0.1% Menthol Glucuronide Solution on Urinary Calcium and Phosphorus Levels, in Milligrams per Liter*

Sample No.	pH	Control Determination		After Equilibration with Calcium Phosphate		After Equilibration with Calcium Phosphate and 0.1% Menthol Glucuronide	
		Calcium	Phosphorus	Calcium	Phosphorus	Calcium	Phosphorus
1	6.2	238.4	770	15.8	540	15.8	540
2	6.5	31.2	520	10.8	500	10.8	500
3	6.8	200.1	455	46.8	395	35.0	400
4	7.9	34.0	100	4.1	90	3.4	75
5	8.9	75.0	450	17.8	420	17.8	410
6	9.2	57.3	970	3.4	970	6.0	980

tion per day or the concentration of calcium and phosphorus per milliliter beyond the range of values that existed before the administration of the drugs. 4. The concentration of organic acids, such as citrates or glucuronides, in urine also have a direct bearing on the solubility product of calcium phosphate. Vermeulen [4] has demonstrated that calcium held in organic union cannot migrate or dialyze.

Although the citrate levels were elevated in some instances after the administration of the drugs, this was not a general effect, as in nearly as many instances the citrate levels were diminished. However, the administration of glucuronolactone and acetylsalicylic acid in all instances raised the concentration of the glucuronides in urine, but the equilibration experiments as described did not demonstrate any direct solubilizing action of the glucuronides on the calcium in urine at pH 6 and at the physiologic concentration used (tables 2 and 3).

TABLE 3.—*Calcium Levels, in Milligrams per Milliliter, in Urine After Equilibration with Calcium Phosphate and Acetylsalicylic Acid*

Sample No.	After Equilibration with: Calcium Phosphate	Calcium Phosphate and Acetylsalicylic Acid, 0.1 Gm.	Increase or Decrease, %	pH
1.....	0.01434	0.01366	—4.78	6.00
2.....	0.0590	0.0328	—44.4	6.18
3.....	0.096	0.077	—19.8	6.25
4.....	0.187	0.150	—19.6	6.50
5.....	0.0480	0.0419	—12.7	6.50
6.....	0.0702	0.0767	+ 9.5	8.00
7.....	0.0108	0.0159	+47.2	8.50
8.....	0.0192	0.0256	+33.35	8.60

Summary

The administration of acetylsalicylic acid and glucuronolactone does not alter the excretion of calcium or any of the factors concerned with its solubility in urine.

451 Clarkson Ave. (Dr. Hamm).

References

1. Elliot, J. S.: Calcium Phosphate Solubility in Urine, J. Urol. **77:**269-274 (Feb.) 1957.

2. Flocks, R. H.: Prophylaxis and Medical Management of Calcium Urolithiasis: Role of Quantity and Precipitability of Urine Calcium, J. Urol. **44:**183-190 (Aug.) 1940.

3. Andrews, J. C.; Yarbro, C. L.; Golby, R. L.; and Sell, I. T.: Studies on Mechanism of Formation of Renal Calculi: I, J. Urol. **73:**930-937 (June) 1955.

4. Vermeulen, C. W.; Miller, G. H.; and Chapman, W. H.: Experimental Urolithiasis: X. On State of Calcium in Urine, J. Urol. **75:**592-601 (April) 1956. Flocks, R. H.: Studies on Nature of Urinary Calcium: Its Role in Calcium Urolithiasis, J. Urol. **64:**633-637 (Nov.) 1950.

5. Prien, E. L., and Walker, B. S.: Salicylamide and Acetylsalicylic Acid in Recurrent Urolithiasis, J. A. M. A. **160:**355-360 (Feb. 4) 1956.

6. Neuberg, C., and Grauer, A.: Enzymatic Cleavage of Conjugated Glucuronic Acids in Relation to Problem of Mineralysis, Enzymologia **15:**115-121 (Nov.) 1951.

7. Cessi, C.: Solubilization of Tricalcium Phosphate During Synthesis of Glucuronide Studied with Radioactive Phosphorus, Boll. Soc. Ital. Biol. Sper. **30:**629-632 (June) 1954.

8. Ravich, R. A., and Ravich, A.: Study of Urinary Surface Tension and Protective Colloids in Urolithiasis: Use of Revici Urotensiometer, J. Urol. **72:**1050-1056 (Dec.) 1954.

9. Rothe, C. F., and Sapirstein, L. A.: Self-standardization Method for Flame Spectrophotometric Determination of Calcium in Biologic Materials, Am. J. Clin. Path. **25:**1076-1089 (Sept.) 1955.

10. Fiske, C. H., and Subba Row, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66:**375-400 (Dec.) 1925.

11. Pucher, G. W.; Sherman, C. C.; and Vickery, H. B.: Method to Determine Small Amounts of Citric Acid in Biological Material, J. Biol. Chem. **113:**235-245 (Feb.) 1936.

12. Fishman, W. H., and others: Investigation of Glucuronic Acid Metabolism in Human Subjects, J. Clin. Invest. **30:**685-696 (July) 1951.

13. Vermeulen, C. W.; Finlayson, B.; and Chapman, W.: Influence of Urinary Glucuronide on Solubility of Calcium Phosphate and Stone Formation: Experimental Urolithiasis: XII, J. Urol. **77:**685-694 (May) 1957.

14. Alpen, E. L.; Mandel, H. G.; Rodwell, V. W.; and Smith, P. K.: Metabolism of C^{14} Carboxyl Salicylic Acid in Dog and in Man, J. Pharmacol. & Exper. Therap. **102:**150-155 (July) 1951.

15. Harlin, H. C., and Wiesel, L.: Modification of Urinary Surface Tension by Oral Glucuronic Acid: Its Application in Prophylaxis of Urinary Calculi, J. Urol. **72:**1046-1049 (Dec.) 1954.

AN INDEFINABLE QUALITY.—Some time ago I read the very moving autobiography of Tenzing of Mount Everest, one of the two first to climb that mountain. He is an unlettered, burly man but still, as Ullman, his collaborator, says, a man possessed of "taste and dignity, courtesy and grace." "There is a flame in Tenzing," says Ullman, "a marvelously strong and pure flame that no storm of man or nature can extinguish. It is compounded of dream and desire, will and struggle, pride and humility; and in the end . . . it is the man's humility that stands out above all his other qualities. In his moment of triumph what he felt in his heart was gratitude to Everest. His prayer for his future life is that it may be worthy of Everest." It is my hope that you can undergird your competence and specialization with this indefinable quality that shows itself in grace and strength and dignity and humility—qualities that can be achieved independently of education. I hope too that you may always have, so to speak, a sense of being worthy of Everest.—Dr. J. R. Killian Jr., The Qualities of a Scientist, (An address given at the awards banquet of the 17th Annual Science Talent Search, in Washington, D. C., March 3), *Science News Letter*, March 15, 1958.

CLINICAL NOTES

PRURITUS FROM AN UNUSUAL SOURCE—BIRD MITES

REPORT OF A CASE

Milton M. Cahn, M.D.
and
Fred R. Shechter, M.D., Philadelphia

Pruritus is always a distressing symptom and may be provoked by many local or systemic factors; however, at times simple causes may be entirely overlooked. Many patients will suffer with an itch of undiagnosed etiology for many weeks, although a battery of clinical and laboratory studies have been done by numerous physicians. This case is reported because of the unusual and rare source of trouble, namely, a bird mite. Once the etiological diagnosis was established, both patient and physician were gratified with the results of simple therapy.

Report of a Case

A 35-year-old female had nocturnal itching of the face, arms, and legs for eight weeks prior to her first visit to us in August, 1957. The itching soon became generalized, and she experienced a crawling and stinging sensation of her skin. She could identify each "sting" by a small black spot that was present at the site. She developed a few small papules and wheals on her skin. The only relief she could obtain was by taking numerous showers day and night. Her husband, her children, and other members of the household were not affected. She was seen by a number of physicians including internists and dermatologists who, after a survey and numerous laboratory studies (blood sugar, complete blood cell counts, urinalyses, serologic test for syphilis, and liver function studies), came to the conclusion that there was nothing organically wrong but that her symptoms were psychosomatic, the latter strongly coloring this patient's history. She was treated for a number of nonexistent dermatological and medical diseases.

When first seen by us, she had already taken numerous tranquilizers. There is no doubt that we too would have missed the diagnosis if a crawling object on her skin had not been found. Also, several specimens of the "black spots" which annoyed her were removed for study. The crawling object was identified as an Arachnid (4 pairs of legs) (fig. 1) and the black spot, which was brown under the microscope, as excrement of this mite. The Arachnid was then further identified by Dr. E. W. Baker of the United States Department of Agriculture as the northern fowl mite, or Ornithonyssus sylviarum (Canestrini and Fanzago, 1877). With the offender known, a systematic search was made to locate the nests where the mite might live, and success was finally achieved when numerous bird nests infested with these mites were found in a window air-conditioner. This served as a perfect means of dissemination. When the air-conditioner was turned on the mites were blown into the room. The patient's husband, who shared the same room, was never affected. The therapy consisted of removing the air-conditioner, thoroughly cleaning the room, and using general hygienic measures.

Associate in Dermatology (Dr. Cahn), and Associate in Medicine (Dr. Shechter), Albert Einstein Medical Center (Southern Division); and from the School of Medicine, University of Pennsylvania (Dr. Cahn), and Hahnemann Medical College (Dr. Shechter).

Comment

Bird and fowl mites (poultry mites) may reside temporarily on the skin of human beings and cause severe pruritus and dermatitis. Such pruritus may give the patient much mental and physical anguish

Fig. 1.—Northern fowl mite (Ornithonyssus sylviarum), × 125.

and the attending physician much harassment. Investigators have reported cases in which such dermatoses have lasted for several years before the cause was discovered.[1] Ticks and mites belong to the class Arachnida. Four pairs of legs are a distinguishing feature. Figure 2[2] represents a classi-

fication of those mites most commonly found on poultry, one of which was responsible for the symptoms in this case. This constitutes only a small proportion of the kind of mites which are parasitic,[3] since there are numerous families and groups. One of the most important mites is the human itch mite —Sarcoptes scabeii.

Ormsby and Montgomery [4] make many references to the occurrences of bird mite dermatitis. They state that, according to Toomey, bird mite dermatitis was first recognized by Redi in 1684. The Arnolds [5] described a case in which only one of two people sleeping in the same room was affected. This resembled our case, in which no one else in the household was involved although they slept in the same room at various times. Sulzberger and Kaminstein [1] described an eruption with severe pruritus especially at night, caused by mites of infested canaries. Schwartz and his colleagues [6] describe a situation in which many workers in an industrial plant were thought to have an occupational dermatitis. After astute "detective" work, many pigeon nests were located. These were infested with bird mites.

The cutaneous reactions are nonspecific. Eruptions may be papular, vesicular, urticarial, or combinations of these, accompanied by excoriations and crusting. Eruptions may occur on any part of the body exposed to the mites. A fact not generally recognized is that in those people who keep themselves clean, no eruptions may appear. In our case lesions were sparse because the patient bathed frequently, day and night. However, pruritus may be profound even in these cases. Dermatitis caused by bird mites may be confused with scabies because both mites provoke symptoms by seeking refuge in dark places and by attacking the host at night. A very important differential diagnostic point from scabies is that the burrow or cuniculus is absent in bird mite dermatitis.

The particular mite in this case (Ornithonyssus sylviarum) infests birds such as swallows, warblers, and canaries and has been reported to harbor the western equine encephalitis virus. Baker and associates [7] point out that in 1947 investigators in California reported recovery of western equine encephalomyelitis virus from mites taken from the nest of the yellow-headed blackbird, but persistence of infection and transmission by bite were not demonstrated. In 1948 there were reports of further isolation of this virus as well as St. Louis encephalitis virus from specimens of northern fowl mite taken from wild bird nests. Baker also states that under experimental conditions Newcastle disease (pneumoencephalitis) was recovered from northern fowl mites that had fed upon sick chickens, but the virus did not persist in the mites.

The significance of the chicken mite (Dermanyssus gallinae) as a possible vector for human disease has also increased recently since the demonstration that it may be a natural vector of eastern equine encephalitis,[8] although there are many references to dispute this.[9] The common chigger (red bug, harvest mite) is capable of causing skin damage in man, and several species are important as vectors of tsutsugamushi fever. Finally, two other animal mites should be mentioned, namely, the tropical rat mite (Ornithonyssus bacoti), a blood-sucking parasite of rats which transmits the rickettsia of endemic typhus, and the mouse mite (Allodermanyssus sanguineus), which transmits the agent of rickettsialpox.

These fowl mites do not reside on the human skin but are merely temporary visitors. Therefore, our patient received no benefit from various antiparasitic treatments applied to the skin. Nor did any of these measures prevent the mites from biting. The only treatment of help was the removal of the source, the infested bird nests. Then a plain soap and hot water bath was sufficient to cure the patient.

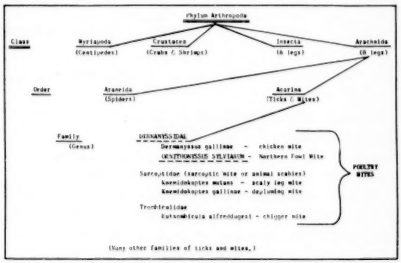


Fig. 2.—Classification of poultry mites.

The control of poultry mites is discussed in a leaflet issued by the United States Department of Agriculture [2] and by Baker and associates.[7] For the control of the northern fowl mite, one of the medicaments they recommend is an insecticide containing malathion, as a dust or spray. They also stress that directions must be carefully followed for most effective use.

Summary

A woman had severe pruritus and mild dermatitis caused by bird mites. The cause was found to be the northern fowl mite (Ornithonyssus sylviarum). A window air-conditioner harbored numerous bird nests infested with this mite. The patient had been extensively studied and was labeled neurotic before the source of the pruritus was found.

Mites may cause dermatitis which is sometimes severe or sometimes insignificant. Animal mites may be the vectors of serious systemic disease. While bird mites are an unusual cause of pruritus,

they should be considered in the differential diagnosis, especially when the patient does not respond to routine therapy.

1930 Chestnut St. (3) (Dr. Cahn).

References

1. Sulzberger, M. B., and Kaminstein, I.: Avian Itch Mites as Cause of Human Dermatoses: Canary Bird Mites Responsible for 2 Groups of Cases in New York, Arch. Dermat. & Syph. **33**:60-72 (Jan.) 1936.

2. Poultry Mites, leaflet 383, U. S. Department of Agriculture, April, 1955.

3. Oman, P. W.: personal communication to the authors.

4. Ormsby, O. S., and Montgomery, H.: Diseases of Skin, ed. 8, Philadelphia, Lea & Febiger, 1954, p. 1294.

5. Arnold, H. L., Jr., and Arnold, H. L.: Diagnosis and Management of Bird Mite Bites, Proc. Staff Meet. Clin., Honolulu **9**:41-44 (May) 1943.

6. Schwartz, L.; Tulipan, L.; and Birmingham, D. J.: Occupational Diseases of Skin, ed. 3, Philadelphia, Lea & Febiger, 1957, p. 676.

7. Baker, E. W., and others: Manual of Parasitic Mites of Medical or Economic Importance, Elizabeth, N. J., National Pest Control Association, 1956, pp. 26-30.

8. Smith, M. H.; Blattner, R. J.; and Heys, F. M.: Further Isolation of St. Louis Encephalitis Virus: Congenital Transfer of Virus in Chicken Mites (Dermanyssus gallinae), Proc. Soc. Exper. Biol. & Med. **59**:136-138 (June) 1945.

9. Reference 7, pp. 12-18.

TRIETHYLENETHIOPHOSPHORAMIDE IN TREATMENT OF METASTATIC CEREBRAL MALIGNANCY

Perk Lee Davis, M.D., Margaret H. Shumway, M.D.
and
Barbara Siu, M.S., Paoli, Pa.

Diabetes insipidus should be considered a symptom. It is usually chronic, but it may be acute and temporary. The case to be reported exemplifies the chronic, secondary type of diabetes insipidus. It was due to metastatic cancer to the pituitary stalk; it was occult but suspected of being malignant and treated as such because of a lack of therapeutic responses with the usual modalities.

Report of a Case

A 68-year-old female had been suffering for six months from diabetes insipidus, diagnosed elsewhere. The lack of response to therapy with vasopressin (Pitressin) tannate in oil and inhalations of posterior pituitary powder as a snuff was responsible for reference to our clinic for evaluation. She had weighed 142 lb. (64.4 kg.) when the symptoms began; she was 62 in. (157.5 cm.) tall and weighed 100 lb. (45.4 kg.) when seen by us. She stated that, for several months before and continuously after the symptoms began, she had vague and occasionally severe pain in the left upper portion of the abdomen and under the ribs in the left lower side of the back. She could, at times, get relief by lying on her abdomen or bending forward. A complete neurological and physical examination was negative except for obvious dryness of the mucous membranes and skin. There was some tenderness on deep pressure over the left upper lateral border of the left side of the rectus muscle and in the left part of the hypochondrium. There were no masses or organ enlargements palpable. Roentgenographic studies of the skull and of the abdominal organs failed to reveal any abnormalities.

Blood and urine chemistry studies were negative. The specific gravity of the urine varied from 1.001 to 1.003. The total daily fluid intake was from 7 to 8 gal., but the urinary output was from 8.5 to 9 gal. daily. Dehydration was becoming progressively worse. Intravenous administration of a hypertonic solution of saline and glucose, inhalations of posterior pituitary powder, injections of vasopressin in oil, and administration of 600 mg. of aminopyrine orally four times daily did not alter the course of the disease.

An intravenous injection of a 2.5% hypertonic saline solution at a rate of 0.25 cc. per kilogram of body weight per minute for 45 minutes showed an increase in the flow of urine, tending to confirm the absence of an antidiuretic hormone. A presumptive diagnosis of occult, metastatic carcinoma to the supraoptic region from a cancer in the tail of the pancreas was made. This diagnosis was suggested because of the abdominal and back pain which was relieved by the prone position or forward bending and because it had preceded and continued after the start of the symptoms of diabetes insipidus.

Accordingly, 40 mg. of triethylenethiophosphoramide (Thio-TEPA) was injected into the right common carotid artery in the same manner used in angiography. There was no untoward reaction. In three days improvement was noted, and in nine days the patient had gradually returned to what appeared to be a normal physiological state. She remarked that the abdominal discomfort was less.

After the ninth day the patient returned to normal and remained well for 5 months and 21 days, with a weight gain to 121 lb. (54.9 kg.). Gradually, she noted a return of increasing thirst, dryness of her mouth, and increasing urination. There was a slight response to therapy with vasopressin in oil if it was given four times daily. This time, 40 mg. of triethylenethiophosphoramide was given in the left common carotid artery. A favorable response began in 4 days and was complete in 11 days. For the next 3 months and 19 days she felt well, but after this she again began taking vasopressin in oil because she felt she needed it. She had been trained, as with a diabetic, to give herself the injections. She kept herself comfortable with vasopressin injections from one to three times weekly for the next two months. She became totally refractory, and 50 mg. of triethylenethiophosphoramide was injected into the right

From the Davis Clinic, Paoli Medical Center.

carotid artery. A remission started in 4 days, but it lasted only for 28 more days. She was given 3,600 r (in air) with use of a 250-kv. machine and a 5-cm. cone. In 10 days a partial remission occurred, which lasted for three more weeks. She became progressively weaker and died.

Postmortem examination revealed a 1-cm. carcinoma of the tail of the pancreas densely adherent posteriorly, but there were no evidences of local metastases. There was a 4-mm. metastasis in the pituitary stalk in the region of the hypothalamic supraoptic nuclei. The tracts had been transected by it. There had been no interference with cerebral fluid dynamics.

Comment

In 1943 and 1951, nitrogen mustard was used in intracarotid injections for treatment of metastatic cerebral malignancy in two cases. One was metastatic carcinoma of the maxillary sinus, and the other was metastatic cancer of the lung. In both instances the convulsions and unconsciousness that followed the injection were as dramatic as the improvement, which lasted three and five months respectively. Nitrogen mustard was not used in this case because of the profound cortical effects witnessed previously. However, the results probably would have been as good.

Summary

An occult cancer of the tail of the pancreas metastasized to the pituitary stalk, causing symptoms of diabetes insipidus. The response of this patient to intracarotid administration of triethylenethiophosphoramide was unusual. Intracarotid administration of nitrogen mustard, used previously in two similar cases, was not attempted because of possibility of profound cortical effects.

Addendum

During the life of the patient reported on and since this paper was submitted, eight patients with cerebral metastases from cancer of the breast and three with cerebral metastases from cancer of the lung have been treated by intracarotid injections of triethylenethiophosphoramide (Thio-TEPA). All were unconscious at the time of initial treatment. Full lucidity and consciousness was regained from four to six hours after the injection. Within six days there was a return of normal activity. In 11 months of use of this therapy, only one patient died; this occurred six months after the first treatment, and autopsy revealed cancer in the brain. All of the remaining patients are alive with cancer. Remissions have been maintained by repeated intracarotid injections of the drug every seven to nine weeks. Local skin metastases respond to local injections into the tumor.

The triethylenethiophosphoramide used in this study was supplied as Thio-TEPA by Dr. James Ruegsegger of the Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

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SPECIAL ARTICLE

A STUDY OF CERTAIN NONPOLIOMYELITIS AND POLIOMYELITIS ENTEROVIRUS INFECTIONS

CLINICAL AND SEROLOGIC ASSOCIATIONS

William McD. Hammon, M.D., Dr. P.H., David S. Yohn, Ph.D.
Ernest H. Ludwig, Ph.D., Rose A. Pavia, B.S., Gladys E. Sather, M.P.H.
and
Lambert W. McCloskey, M.S., Pittsburgh

Recently the term "enteroviruses" was introduced as descriptive of a large group of human viruses which includes the three polioviruses, the Coxsackie viruses, and the ECHO viruses.[1] These agents have many properties in common, including the ability to multiply in the human gastrointestinal tract with or without the production of clinical disease. Disease, when it does occur, most frequently involves the central nervous system (CNS). Classification of the enteroviruses into the three groups listed above has become more difficult as certain properties originally believed unique for one group are found to be shared by others. Further evidence of common pathogenic and serologic properties are presented in this communication.

Numerous nonpoliomyelitis enteroviruses have been associated with aseptic meningitis, a subject recently reviewed by others.[2] A few paralytic illnesses have also been reported which were associated with nonpoliomyelitis enterovirus infections,[3] and some in combination with a poliovirus.[4] Present data indicate that Coxsackie A-7,[5] ECHO-2,[3e] ECHO-6,[6] ECHO-9,[7] and some Coxsackie B [8] viruses may cause paralytic illness resembling poliomyelitis clinically. This report contains further

From the Department of Epidemiology and Microbiology, Graduate School of Public Health, University of Pittsburgh. Dr. Ludwig is now at the Department of Bacteriology, Pennsylvania State University, University Park, Pa.

evidence that certain other members of the Coxsackie and ECHO groups may or actually do cause mild paralysis.

Six paralytic cases from the gamma globulin field trials of 1952 [9] are discussed, the etiologies of which have been examined as thoroughly as possible. In addition, 10 nonparalytic poliomyelitis-like illnesses (aseptic meningitis) and five healthy individuals, each infected with a nonpoliomyelitis enterovirus, are described. The latter five infections, together with some of the others, show a broad serologic response by complement fixation which suggests minor antigenic relationships between certain nonpoliomyelitis and poliomyelitis enteroviruses.

Materials and Methods

Cell Culture.—Monolayer cell cultures of trypsinized rhesus monkey kidney were used in isolation studies, neutralization tests, and preparation of complement-fixing antigens. Prior to December, 1956, medium 199 was used as fluid phase. By this time it was evident that lactalbumin hydrolysate in Earle's balanced salt solution with 0.5% calf serum generally maintained cell cultures and supported viral multiplication as well as did medium 199, possessed greater buffering capacity, and was more economical to prepare. Mediums employed prior to October, 1956, contained 400 units of penicillin and 0.2 mg. of streptomycin per milliliter. Thereafter 20 units of polymyxin and 25 units of nystatin (Mycostatin) were also added to each milliliter.

Virus Isolation.—The methods employed for the laboratory examination of the specimens from the gamma globulin field studies of 1952 have been described previously.[9b] Fecal specimens or rectal swabs obtained from patients of the 6208th U. S. Air Force Hospital at Clark Air Force Base (CAFB) in the Philippine Islands were tested for virus in the same manner. Viruses were identified in neutralization tests with antiserums specific for Coxsackie, ECHO, and polioviruses. Materials from which an ECHO virus was isolated were also tested for Coxsackie viruses in day-old suckling mice through three blind passages.

Serology.—Neutralizing antibody (NA) tests were performed on all serums from one subject simultaneously. Fourfold dilutions beginning at 1:4 were employed. Equal volumes of virus, 100 tissue culture infective doses ($TCID_{50}$) per 0.1 ml., and serum dilution were mixed and incubated one hour at room temperature; 0.2 ml. was added to each of two monkey kidney cell cultures. Control titrations of each virus were performed simultaneously to determine the actual test dosage. Results were expressed as the reciprocal of that serum dilution calculated by the method of Reed and Muench [10] to protect 50% of the inoculated cell culture tubes.

Poliovirus complement-fixation (CF) tests were carried out by a modification [11] of the Fulton and Dumbell plate method [12] with use of heat-inactivated cell culture antigens which had been prepared by the concentration technique described by Svedmyr, Enders, and Holloway.[13] Results are expressed as the reciprocal of the highest serum dilution which gave a 2+ reaction in the presence of two units of complement and two units of antigen. Antigens were prepared and the majority of CF tests were performed prior to February, 1955.

Clinical Diagnosis.—Paralytic cases which occurred during the gamma globulin field studies were classified quantitatively on the basis of graded muscle weakness. A detailed account of this method of scoring and its applications was reported previously.[9a] A clinical diagnosis of paralytic disease was accepted only when there were characteristic physical findings and history together with definite weakness of one or more muscles in the absence of pain, muscle spasm, or other explanatory cause. Muscle involvement data reported herein represent the degree of residual muscle weakness at the 60-day examination. The highest possible score in the event of complete paralysis of all muscles was 560. A diagnosis of nonparalytic poliomyelitis (aseptic meningitis) was made only in the presence of positive cerebrospinal fluid findings, associated with clinical manifestations and a typical history. The basis for the clinical diagnosis of nonparalytic poliomyelitis or aseptic meningitis in patients from CAFB was obtained from abstracts of clinical records forwarded from the Philippines.

Laboratory Diagnosis.—Quantitative poliovirus NA and CF tests were made on all serum specimens. In the absence of a significant NA rise to any of the three polioviruses, all tests were repeated. In those instances in which a nonpoliovirus was isolated and serum was available, NA tests were performed against the virus isolated. With serums of patients from CAFB, NA tests were also carried out against ECHO 1, 12, and 13 and Coxsackie A-9 viruses. These agents had been shown in a previous study by Hammon and co-workers [14] to be producing infections in this area. Hemagglutination-inhibition tests with Japanese B encephalitis, mumps, and influenza viruses as well as CF tests against the virus of lymphocytic choriomeningitis were occasionally included in the serologic examination of CAFB patients. These latter four tests were carried out at the U. S. Army's 406th Medical General Laboratory in Japan.

Final laboratory diagnosis was based on virus isolation and confirmation of serologic data when available. In the absence of a virus isolation, an increase in NA titer of fourfold or greater was considered significant and indicative of infection, as was an increase from $<1:4$ to 1:8 or more. CF rise alone was not accepted as diagnostic for polio-

myelitis since heat-inactivated cell culture antigens occasionally gave titer rises in instances in which all other data indicated that no poliovirus infection had occurred. Several others [15] have reported similar findings.

Findings

Paralytic Cases Without Poliovirus Infection.—No laboratory evidence of a poliovirus infection was found in three patients whose illnesses could not be differentiated clinically from paralytic poliomyelitis. In each instance a Coxsackie virus was isolated. A significant serologic response was demonstrated to the virus isolated in two cases examined (table 1). All three cases are described below.

Iowa-53.—During the first week after the onset of a paralytic illness Coxsackie B-4 virus was isolated from the feces of this 4-year-old boy, who had been inoculated with gelatin placebo. A serum specimen taken on the fourth day revealed the presence of NA to types 1 and 3 polioviruses but not to the virus isolated (table 1). Two additional specimens, obtained approximately five and nine weeks later, showed no significant change in poliovirus serology, whereas a significant NA increase, from <1:4 to 1:32, occurred to the Coxsackie B-4 virus during the first five weeks of illness.

These results indicate that this individual had had a previous experience with type 1 and 3 polioviruses and that the present illness was probably the result of the Coxsackie virus infection.

Iowa-102.—During the first week of paralytic illness a Coxsackie B-3 virus was isolated from the feces of this 2-year-old noninjected girl and also from her 3-year-old gelatin-injected healthy sister. The NA and CF titers of all three serum specimens collected from both girls, 2, 32, and 68 days after onset of illness in the patient, were less than 1:4 to all three types of poliovirus (table 1). Serologic studies on the healthy sibling are not shown. In contrast with the poliovirus serology, both girls showed a fourfold NA rise and fall to their respective B-3 viruses.

These serologic findings show that this illness could not be attributed to a poliovirus infection. The only apparent conclusion is that this disease was the result of the Coxsackie B-3 infection.

Texas-197.—The third patient was a 4-year-old noninjected male from whom Coxsackie A-9 virus was isolated early in the paralytic disease. Although a high NA titer, 1:1,024, and a CF titer of 1:8 to type 1 poliovirus were present at onset, no significant serologic changes to any of the three polioviruses occurred during the following two months. Coxsackie A-9 virus was also isolated at the same time from two healthy siblings of the patient. Their poliovirus serology was identical with that of the patient. No poliovirus was isolated from either of these children. Because of repeated serologic tests with polioviruses, all serum specimens were exhausted and could not be tested against the A-9 virus isolated.

There remains little doubt that the A-9 infection and disease were related and that the type 1 poliovirus antibodies were evidence of an earlier experience with that virus.

Paralytic Cases Probably Without Poliovirus Infection.—Three paralytic patients from whom no poliovirus could be isolated demonstrated suspicious poliovirus CF findings without significant changes in NA during the two months after onset of illness. In each instance an ECHO virus was isolated and a serologic response (NA) demonstrated to the isolated virus (table 2).

Iowa-97.—Type 16 ECHO virus was isolated from a pool of feces of this 11-year-old gamma globulin–inoculated paralyzed girl. The feces were collected between the sixth and ninth day after onset. A serum sample taken on the fifth day contained NA to all three polioviruses, but not to the virus isolated. The second specimen taken a month later neutralized ECHO-16 virus in a dilution of 1:8 while poliovirus NA titers did not change. However, the CF titers to all three polioviruses rose eightfold to sixteenfold during this interval. This latter observation is suggestive of the CF group reaction which is commonly found with heat-inactivated poliovirus antigens during some poliovirus infections, especially when the current infection has been preceded by experience with one or more polioviruses.

Whether the CF rise in Iowa-97 was caused by the ECHO-16 virus infection cannot be determined. The lack of a rise or fall in NA titers to any of the three polioviruses, their relatively modest titers,

TABLE 1.—*Cases of Clinical Paralytic Poliomyelitis-like Disease Without Evidence of Concurrent Poliovirus Infection but Associated With Coxsackie Virus Isolation*

Area and Case	Age and Sex	60-Day Muscle Score	Virus Isolation: Type	Virus Isolation: Day*	Day of Serum Specimens*	Serology†: Poliovirus 1 NA	Poliovirus 1 CF	Poliovirus 2 NA	Poliovirus 2 CF	Poliovirus 3 NA	Poliovirus 3 CF	NA to Virus Isolated	Etiology: Laboratory Methods
					4	16	<4	<4	4	256	32	<4	
Iowa-53	4-M	4.75	Coxsackie	5-7	35	8	<4	<4	8	128	16	32	Coxsackie
			B-4		60	8	<4	<4	8	128	16	...	B-4
					2	<4	<4	<4	<4	<4	<4	64	
Iowa-102	2-F	16.5	Coxsackie	3-6	32	<4	<4	<4	<4	<4	<4	256	Coxsackie
			B-3‡		68	<4	<4	<4	<4	<4	<4	64	B-3
					2	1,024	8	<4	<4	<4	<4	...	
Texas-197	4-M	3.0	Coxsackie	3,10	31	2,048	8	<4	<4	<4	<4	...	Coxsackie
			A-9§		60	2,048	8	<4	<4	<4	<4	...	A-9

* Day specimen obtained after onset of illness.
† NA = neutralizing antibody; CF = complement-fixing antibody.
‡ Also isolated from one well sibling.
§ Also isolated from two well siblings.

and our failure to isolate a poliovirus suggest that the CF rise was not the result of a current poliovirus infection. Further instances of the CF group reaction will be noted later.

The evidence that this paralytic disease was the result of the ECHO-16 infection is not conclusive. However, ECHO-16 has been shown to produce meningeal pleocytosis in monkeys after intrathecal injection,[16] and in man it has been associated with aseptic meningitis and an exanthem.[17] It is of interest to note that gamma globulin failed to protect this child against the CNS disease probably caused by ECHO-16.

Texas-123.—During the first week of illness ECHO-4 virus was isolated from the stool of this gamma globulin–inoculated 3-year-old boy, as well as from the feces of a well sibling. NA and CF antibodies to all three types of poliovirus were present in relatively low titer at the onset of illness while no NA was found for ECHO-4 virus. Two additional serum specimens, which were obtained at consecutive four-week intervals, showed only a twofold rise in type 2 poliovirus NA titer followed by a fourfold fall; these variations are within the possible range of error of the method. CF antibodies to all three polioviruses were present but showed no significant changes. On the other hand, ECHO-4 NA increased from <1:4 to 1:16 and then receded to 1:4.

Nearly five weeks later the ECHO-4 NA titer had risen to 1:128, whereas no changes were noted in poliovirus NA levels. During this same interval, CF titers to all three polioviruses decreased twofold to fourfold and, as shown in table 2, continued to decline at about the same rate for the next four weeks. During this latter interval the ECHO-4 NA titer receded to <1:10.

Herein is another example of a poliovirus CF group reaction, the cause of which cannot be determined with certainty. Whether the CF changes were related to the ECHO-4 infection and accompanying immunological response is not known. A similar CF finding was not noted in the preceding ECHO-4 infection, Texas-123. The findings in both Texas-123 and Texas-175 are evidence that ECHO-4 may cause paralytic illness.

Cases of Aseptic Meningitis Associated with Nonpoliomyelitis Enterovirus Infections.—As a result of virus isolation and serologic studies, we have selected for presentation 10 patients with aseptic meningitis who were found to be infected with a nonpoliomyelitis enterovirus. Three of the cases selected, Texas-31, Texas-192, and Iowa-123, were from the gamma globulin field trial. Texas-31 had received gamma globulin. The remaining seven were patients at CAFB, Philippine Islands. In five instances, a nonpoliomyelitis enterovirus was isolated from fecal material (table 3). Three isolations of ECHO-4, one in the child given gamma globulin and one each of ECHO-3 and Coxsackie B-4, were made. In the five remaining individuals (table 4) extensive serologic tests revealed the presence of two Coxsackie A-9 infections; two of ECHO-1, one of which occurred in conjunction with an ECHO-12; and one of ECHO-13.

In serums from 9 of the 10 patients no significant increase in poliovirus NA titers occurred during the course of illness. In the 10th patient, CAFB-DJ, NA titers to types 1 and 2 poliovirus rose to only 1:8 and fell promptly to the original <1:4 level, a serologic finding not characteristic of true poliovirus infection.

Table 2.—*Cases of Clinical Paralytic Poliomyelitis-like Disease with Doubtful Evidence of Concurrent Poliovirus Infection but with ECHO Virus Isolation*

Area and Case	Age and Sex	60-Day Muscle Score	Virus Isolation		Day of Serum Specimens*	Serology†						NA to Virus Isolated	Etiology: Laboratory Methods
						Polioviruses							
						1		2		3			
			Type	Day*		NA	CF	NA	CF	NA	CF		
Iowa-97	11-F	1.0	ECHO	6-9	5	128	<4	8	8	128	32	<4	
			16		37	128	16	8	128	256	256	8	ECHO
					60	128	8	8	64	64	256	8	16
Texas-123	3-M	3.0	ECHO‡	3-4	1	32	32	8	16	64	16	<4	
			4		30	32	16	16	16	64	8	16	ECHO
					57	32	16	4	16	128	8	4	4
Texas-175	3-F	2.5	ECHO	4-7	4	64	64	<4	16	128	32	8	
			4		37	64	16	<4	8	128	16	128	ECHO
					64	64	8	<4	<4	128	8	<16	4

* Day specimen was obtained after onset of illness.
† NA = neutralizing antibody; CF = complement-fixing antibody.
‡ Also isolated from a well sibling.

The above serologic findings together with the isolation of only ECHO-4 suggest strongly that this paralytic illness was the result of the ECHO-4 infection. ECHO-4 has not been associated previously with paralytic illness; however, it has been isolated from patients with aseptic meningitis and exanthem.[18] So far, extensive studies on the neurotropic properties of ECHO-4 in other primates have not been reported. As in the previous case, gamma globulin did not afford protection.

Texas-175.—The third case in this section is similar to the preceding one. ECHO-4 virus was isolated from the feces of this 3-year-old gelatin-injected girl during the latter portion of the first week of illness. NA to polioviruses types 1 and 3 and CF antibodies to all three types were present in a serum specimen taken on the fourth day after onset. At this time, the NA titer for the homologous ECHO-4 virus was 1:8.

Serums from Iowa-123 from whom ECHO-4 was isolated during the acute phase of illness (table 3) gave persistent, relatively high poliovirus type 1 (ca 1:2,048) and, to a lesser degree, type 3 (ca 1:256) NA titers, while CF titers to all three polioviruses were falling during the observation period (table 3). These findings suggest that either a type 1 poliovirus infection preceded the ECHO-4 infection or that the latter infection elicited a serologic response in the form of a poliovirus CF group reaction. Even though this illness occurred during a poliomyelitis type 1 outbreak,[19] it seems reasonable to believe that ECHO-4 was etiologically involved because only ECHO-4 was isolated and it has been formerly associated with aseptic meningitis.[20]

A poliovirus group CF response also occurred in CAFB-SJ who, as shown in table 4, gave serologic evidence of a simultaneous infection with ECHO viruses 1 and 12. In this latter connection a pool of ECHO-12 hyperimmune monkey antiserums prepared by Dr. Herbert Wenner [1b] has been found to neutralize ECHO-1 virus in dilutions one-hundredfold less than the homotypic end point. The converse has not been found, and similar results have not been obtained with lower titered ECHO-12 antiserums. In view of the above findings, which have been confirmed in at least three other laboratories, it appears improbable that the appearance of NA to ECHO-1 in CAFB-SJ was the result of only an ECHO-12 infection. Furthermore, in three other ECHO-12 infections studied, one of which is shown in table 5 as 2-85, a significant serologic response to ECHO-12 was not accompanied by an increase in NA titer to ECHO-1. Although it is likely that dual infection with ECHO viruses 1 and 12 occurred in CAFB-SJ, the cause of this illness cannot be established since there are three etiological possibilities—ECHO-1 alone, ECHO-12 alone, or both together.

Nonpoliovirus Infection in Healthy Individuals.—Table 5 presents the results of tests for viruses and of the serologic examinations of five healthy individuals found to be infected with a nonpoliomyelitis enterovirus. These individuals were selected from the longitudinal survey of American families in the Philippines [14] to further illustrate the appearance of an occasional CF reaction to heat-inactivated poliovirus antigens during the immunological response to another enterovirus.

In one instance a 2-year-old girl, 1-163, who had had an earlier experience with type 1 poliovirus, was found to be infected with ECHO-4 and Coxsackie B-3 and B-4. Each of these three viruses was isolated in sequence and neutralizing antibodies to each were developed. A significant rise in types 2 and 3 poliovirus CF antibodies was demonstrated even though no NA to either type was detected during the observation period (table 5). The CF antibody rise was associated in time with the ECHO-4 infection and antibody response. Two other individuals, 1-186 and 2-47, from whom ECHO-1 was isolated, exhibited concurrent increases in NA to ECHO-1 and CF antibodies to type 3 poliovirus. In neither instance was there any evidence of NA to any of the three types of poliovirus. A fourth person, 2-85, who was infected with ECHO-12, showed an increase in ECHO-12 NA from <1:4 to 1:128 and concurrently fourfold to eightfold increases in CF antibodies for all three polioviruses. The serologic response of 2-86, who was also infected with ECHO-12, was similar to that of the sibling 2-85, except that no change was noted in the CF titer to type 1 poliovirus. Both 2-85 and 2-86 exhibited no significant change in type 2 poliovirus NA titers, the only type to which NA was demonstrated.

TABLE 3.—*Cases of Aseptic Meningitis and Results of Laboratory Studies for Etiology*

Area and Case	Age and Sex	Virus Isolation: Type	Virus Isolation: Day*	Day of Serum Specimens*	Serology† Polioviruses: 1 NA	1 CF	2 NA	2 CF	3 NA	3 CF	NA to Virus Isolated	Etiology: Laboratory Methods
Texas-31	4-M	ECHO-4	8-11	6	<4	<4	<4	<4	<4	<4	<4	ECHO-4
				58	<4	<4	<4	<4	<4	<4	8	
Iowa-123	4-M	ECHO-4	1,8	2	2,048	>256	<4	128	512	64	Serum exhausted	ECHO-4
				27	4,096	64	<4	64	256	32		
				60	1,024	32	<4	16	256	16		
CAFB-ER	23-M	ECHO-4	2	2	512	<4	8	4	128	4	Serum exhausted	ECHO-4
				15	128	...	8	...	64	...		
CAFB-RC	7-M	ECHO-3	17	12	512	<4	<4	8	<4	<4	Serum exhausted	ECHO-3
				47	512	<4	<4	4	<4	<4		
Texas-192	3-M	Coxsackie B-4	9-11	9	256	<4	<4	<4	<4	<4	16	Coxsackie B-4
				36	128	<4	<4	<4	<4	<4	128	
				64	128	<4	<4	<4	<4	<4	64	

* Day specimen was obtained after onset of illness.
† NA = neutralizing antibody; CF = complement-fixing antibody.

Comment

Initially this discussion will be concerned with the six paralytic illnesses which apparently were not due to a poliovirus infection (tables 1 and 2).

It should be emphasized that these illnesses had been diagnosed as clinical paralytic poliomyelitis by a team of experienced poliomyelitis clinicians engaged in a research evaluation.[9a] We refer to these illnesses now as paralytic poliomyelitis-like because there is essentially no laboratory evidence of a poliovirus infection. This distinction is made because of the formerly held concept that this type of paralytic disease is only caused by one of the three types of poliovirus.

Whether the enteroviruses isolated in all six cases were the respective etiological agents is not unequivocally established. The fact that virus was isolated from the feces during the acute phase of illness and its presence was followed, in the five cases in which the serums were tested, by a significant serologic response to the virus isolated, establishes the temporal relationship between onset of infection and onset of disease.

In the past, the demonstration of a poliovirus infection during the acute phase of illness, as established by isolation of the virus from the feces or by serological means, has been accepted as diagnostic. This acceptance was based on the knowledge that these viruses infect the intestinal tract of man, produce a typical pathology in fatal cases, and produce similar pathology in other primates when infected experimentally. With the exception of Coxsackie B-3,[21] none of the five enteroviruses involved in these paralytic illnesses has been reported to produce fatal CNS disease in man. Thus, human CNS pathology as a result of infection with four of these viruses, ECHO-4, ECHO-16, and Coxsackie A-9 and B-4, is not known. Furthermore, experimental paralytic disease has not been reported in primates with these five viruses. This may be attributed in part to the lack of adequate testing with a large number of strains. For example, after the "Russian Poliovirus Type 4" [9b] was identified as a Coxsackie A-7, Habel and Loomis [9a] found that two American strains of Coxsackie A-7 also produced "CNS lesions identical with severe poliomyelitis" in monkeys when inoculated intracerebrally. Coxsackie B-3 has been reported by Kibrick and Benirschke [21] as having produced CNS lesions in the spinal cord and the myocardium of one infant who died of the disease.

Other strains of ECHO-4 and ECHO-16 and Coxsackie A-9, B-3, and B-4 have been isolated from patients with aseptic meningitis and are acknowledged etiological agents of this syndrome.[22]

TABLE 4.—*Cases of Aseptic Meningitis and Results of Laboratory Studies for Etiology*

Area and Case	Age and Sex	Virus Isolation: Type	Virus Isolation: Day*	Day of Serum Specimens*	Serology† Polioviruses 1 NA	1 CF	2 NA	2 CF	3 NA	3 CF	Other Virus NA	Etiology: Laboratory Methods
											ECHO-13	
				3	<4	<4	<4	8	64	4	8	
CAFB-MJ	11-F	None	2	16	<4	<4	<4	8	64	<4	32	ECHO-13
				42	<4	<4	<4	16	64	<4	8	
											Coxsackie A-9	
				4	<4	<4	<4	4	16	<4	16	
CAFB-DJ	23-M	None	6	18	8	<4	8	16	8	8	64	Coxsackie
				48	<4	<4	<4	16	16	8	64	A-9
											Coxsackie A-9	
CAFB-BG	22-M	None	3	5	<4	...	128	...	<4	...	64	Coxsackie
				29	<4	...	128	...	<4	...	256	A-9
											ECHO-1	
				2	8	<4	<4	16	16	16	32	
CAFB-QW	29-M	None	2	15	4	4	<4	32	32	32	1,024	ECHO-1
				54	4	<4	<4	32	16	32	128	
											ECHO-1 ECHO-12	
				2	64	<4	<4	8	16	<4	<4 <4	ECHO-12
CAFB-SJ	27-M	None	7	14	128	8	<4	32	8	8	16 32	and
				54	128	4	<4	16	8	8	4 4	ECHO-1

* Day specimen was obtained after onset of illness.
† NA=neutralizing antibody; CF=complement-fixing antibody.

It seems justifiable to expect instances in which the combination of unusual viral invasiveness and/or host susceptibility results in progression of the disease with the involvement of motor neurons as in poliomyelitis. In other words, there may exist strains of enteroviruses which, with opportune conditions, act like polioviruses in man and produce an occasional paralytic illness that clinically cannot be differentiated from paralytic poliomyelitis. We feel that these six cases are examples of the occasional paralytic illness caused by a nonpoliomyelitis enterovirus. Others, previously reported, were cited above.

Ten cases of aseptic meningitis were described which were associated with nonpoliomyelitis enterovirus infections. These viruses were ECHO types 1, 3, 4, 12, and 13 and Coxsackie A-9 and B-4. Only ECHO viruses 1, 12, and 13 have not been associated by others with CNS disease. However,

Hammon and co-workers [14b] previously pointed out suggestive evidence of the etiological role of ECHO-1 and ECHO-12 in connection with another group of patients. Thus the list of viruses which are probably involved in CNS disease becomes even longer and the evidence of etiology more convincing.

These paralytic and nonparalytic illnesses cannot be expected to be prevented by the present poliomyelitis vaccine and may be considered vaccine failures unless the exact etiology is established. Three of these were also noted as gamma globulin failures. The laboratory results reported herein emphasize the importance of complete etiological study of paralytic and nonparalytic poliomyelitis-like disease.

Considerable CF work has been performed in the past with heat-inactivated poliovirus antigens. Our experience with this type of preparation has been extensive over a number of years, over 4,000 tests having been performed. These antigens have proved useful, but frequently the results have been difficult to interpret. Not only did they occasionally give evidence of a CF group reaction in the presence of a poliovirus infection but also occasionally demonstrated a significant poliovirus CF reaction in the absence of a poliovirus infection but in the presence of another enterovirus infection. Ten out of many instances of a poliovirus CF response in the presence of another nonpoliomyelitis enterovirus infection have been presented. The viruses involved included ECHO types 1, 4, 12, and 16 and Coxsackie type A-9. It may be suggested that what we have demonstrated is merely an anamnestic reaction mediated by the infecting virus. This possibility cannot be overlooked in the eight instances in which NA was present to one or more polioviruses at the onset of illness. However, in two "triple negatives" who were infected with ECHO-1 (table 5) this concept is much less tenable. It seems more likely that the CF responses observed in all 10 cases resulted from minor antigenic relationships between these nonpoliomyelitis and poliomyelitis enteroviruses which are apparently demonstrated only by CF reactions with heat-inactivated poliovirus antigens. It should be noted that three of these reactions occurred during infection by ECHO-4. Further studies should be made of this phenomenon. Unfortunately animal experiments have not proved to be appropriate means, since the group antigenic relationship even between polioviruses has been demonstrable only in man.

At present the serologic associations demonstrated here lend strong support to the concept of common antigens between poliomyelitis and nonpoliomyelitis enteroviruses as revealed by this type of CF procedure, thus justifying its continued use to acquire more such data. However, it is obvious that heat-inactivated monkey kidney cell culture antigens are not satisfactory when the CF test is used alone for the specific diagnosis of poliomyelitis. Several other more specific antigens are now available for this latter purpose, but because of their greater type specificity, their use cannot be expected to throw more light on the intriguing problem of common antigens.

It becomes more apparent through these series of patients and normal persons presented above that two properties which up to recently have been considered unique for polioviruses, at least insofar as the enterovirus group was concerned, are shared by the Coxsackie and ECHO viruses. The first of

TABLE 5.—*Serologic Studies of Five Healthy Persons Infected with Nonpoliomyelitis Enteroviruses*

No. of Case	Age and Sex	Virus Isolation: Type	Virus Isolation: Day*	Day of Serum Specimens*	Serology†: Polioviruses 1 NA	1 CF	2 NA	2 CF	3 NA	3 CF	NA to Virus Isolated: E-4	B-3	B-4
		ECHO-4	59	0	**1,024**	<4	**<8**	8	**<8**	<4	**<2**	**<4**	**<4**
1-163	2-F	Coxsackie B-3	87	59	...	<4	**<8**	64	**<8**	32	**8**	**<4**	**<4**
		Coxsackie B-4	118	118	**1,024**	<4	**<8**	64	**<8**	16	**>256**	**16**	**32**
				0	**<4**	<4	**<4**	<4	**<4**	<4		**16**	
1-186	3-M	ECHO-1	44	56	**<4**	<4	**<4**	<4	**<4**	8		**>256**	
			121	121	**<4**	<4	**<4**	<4	**<4**	8		**128**	
				0	**<4**	8	**<4**	16	**<4**	16		**<4**	
2-47	29-F	ECHO-1	28	28	**<4**	8	**<4**	16	**<4**	32		**4**	
				84	**<4**	8	**<4**	32	**<4**	64		**64**	
				0	**<4**	8	**64**	16	**<4**	16		**<4**	
2-85‡	6-M	ECHO-12	14	28	**<4**	32	...	128	**<4**	64		**128**	
				84	**<4**	8	**128**	16	**<4**	8		**32**	
				0	**<4**	<4	**128**	8	**<4**	<4		**<8**	
2-86‡	3-F	ECHO-12	28	110	**<4**	<4	**128**	>16	**<4**	16		**128**	

* Collection day after first serum specimen.
† NA=neutralizing antibody; CF=complement-fixing antibody.
‡ Siblings (2-85 and 2-86).

these properties is paralytic disease manifestations illustrated here by six cases, and the second is antigenic constitution, as demonstrated by serology in at least 10 instances. No claim is made that any single case or normal person in this series presents conclusive evidence of pure infection by a single ECHO or Coxsackie virus and that the disease occurring or the serologic findings were the result of such single infection. However, it is considered probable that such is the case for the majority. This evidence, together with previous data summarized from a variety of sources, supports these conclusions. This raises a question regarding the justification for continuing to call members of the enteroviruses by three different generic-like names, as more and more of their bases for original definition and classification are found to be shared rather than confirmed as distinct or unique.

Summary

Laboratory studies on the etiology of 6 paralytic poliomyelitis-like illnesses and 10 cases of aseptic meningitis established essentially no evidence of poliomyelitis virus infection, by either isolation or serologic methods. The probable etiological agents of the paralytic illnesses were shown to be Coxsackie viruses A-9, B-3, and B-4 and ECHO viruses 4 and 16. Gamma globulin failed to protect against the central nervous system disease apparently produced by ECHO-4 and ECHO-16 viruses. The viruses associated with aseptic meningitis were Coxsackie types A-9 and B-4 and ECHO types 1, 3, 4, 12, and 13.

In five of the above illnesses attributed to ECHO or Coxsackie viruses serologic studies revealed the presence of a CF response to heat-inactivated monkey kidney cell culture poliomyelitis antigens. Similar findings were presented for five healthy individuals, also infected with nonpoliomyelitis enteroviruses. It is suggested that these immunological responses are the result of minor common antigens. The viruses apparently eliciting this response in man included Coxsackie type A-9 and ECHO types 1, 4, 12, and 16. It is concluded therefore that certain ECHO and Coxsackie viruses not only overlap with polioviruses in their pathological effects on the central nervous system, in a manner believed formerly to be essentially unique for polioviruses, but also they bear antigenic relationships to polioviruses. Thus, these three groups of agents become less distinct and become progressively more difficult to define and justify as members of separate generic-like classifications.

130 DeSoto St., Pittsburgh (13) (Dr. Hammon).

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

Technical assistance in this study was given by Miss Della M. Whitaker.

Crude virus suspensions for concentration were obtained from Dr. William Wood, Connaught Medical Research Laboratories, University of Toronto, Canada.

References

1. Committee on ECHO Viruses: (*a*) Enteric Cytopathogenic Human Orphan (ECHO) Viruses, Science **122:**1187-1188 (Dec.) 1955. (*b*) Committee on Enteroviruses: The Enteroviruses, Am. J. Pub. Health **74:**1556-1566 (Dec.) 1957.

2. (*a*) Dalldorf, G.: Brief Review of Coxsackie Viruses in 1956, Ann. New York Acad. Sc. **67:**209-211 (April 19) 1957. (*b*) Habel, K.; Silverberg, R. J.; and Shelokov, A.: Isolation of Enteric Viruses from Cases of Aseptic Meningitis, ibid. **67:**223-229 (April 19) 1957. (*c*) Meyer, H. M., Jr.; Rogers, N. G.; Miesse, M. L.; and Crawford, I. P.: Aseptic Meningitis Caused by Orphan Viruses and Other Agents, ibid. **67:**332-337 (April 19) 1957. (*d*) Parrott, R. H.: Clinical Importance of Group A Coxsackie Viruses, ibid. **67:**230-240 (April 19) 1957. (*e*) Rhodes, A. J., and Beale, A. J.: Aseptic Meningitis: Evidence for Etiologic Role of Coxsackie B and "Orphan" Viruses, ibid. **67:**212-222 (April 19) 1957. (*f*) Melnick, J. L.: ECHO Viruses, in Cellular Biology, Nucleic Acids and Viruses, Special Publications of New York Academy of Sciences **5:**365-392 (Dec.) 1957.

3. (*a*) Habel, K., and Loomis, L. N.: Coxsackie A-7 Virus and Russian "Poliovirus Type 4," Proc. Soc. Exper. Biol. & Med. **95:**597-605 (July) 1957. (*b*) Chumakov, M. P., and others: Problems of Virology, vol. 1, p. 16, 1956; cited by Habel and Loomis.[3a] (*c*) Steigman, A. J., in discussion on Part 1: Coxsackie Viruses, G. Dalldorf, Chairman, Ann. New York Acad. Sc. **67:**249-250 (April 19) 1957. (*d*) Kibrick, S.; Meléndez, L.; and Enders, J. F.: Clinical Associations of Enteric Viruses with Particular Reference to Agents Exhibiting Properties of ECHO Group, ibid. **67:**311-325 (April 19) 1957. (*e*) Karzon, D. T.; Barron, A. L.; Winkelstein, W., Jr.; and Cohen, S.: Isolation of ECHO Virus Type 6 During Outbreak of Seasonal Aseptic Meningitis, J. A. M. A. **162:**1298-1303 (Dec. 1) 1956. (*f*) Sabin, A. B.; Krumbiegel, E. R.; and Wigand, R., to be published. (*g*) Baumann, T., and others: Erkrankungen durch ECHO-Virus Type-9: Eine epidemiologische, klinische und virologisch-serologische Studie, Schweiz. med. Wchnschr. **87:**307-315 (March 30) 1957. (*h*) Verlinde, J. D.: Discussion presented at Fourth International Poliomyelitis Conference, Geneva, Switzerland, 1957, to be published.

4. Melnick, J. L., and others: Epidemic of Paralytic Poliomyelitis Characterized by Dual Infections with Poliomyelitis and Coxsackie Viruses, J. Exper. Med. **94:**471-492 (Dec.) 1951.

5. References 3*a* and *b*.

6. References 3*d* and *e*.

7. References 3*f*, *g*, and *h*.

8. References 1*b*, 3*c*, and 4.

9. (*a*) Hammon, W. M.; Coriell, L. L.; Wehrle, P. F.; and Stokes, J., Jr.: Evaluation of Red Cross Gamma Globulin as Prophylactic Agent for Poliomyelitis: 4. Final Report of Results Based on Clinical Diagnosis, J. A. M. A. **151:**1272-1285 (April 11) 1953. (*b*) Hammon, W. M., and others: Evaluation of Red Cross Gamma Globulin as Prophylactic Agent for Poliomyelitis: 5. Reanalysis of Results Based on Laboratory-Confirmed Cases, ibid. **156:**21-27 (Sept. 4) 1954.

10. Reed, L. J., and Muench, H.: Simple Method of Estimating 50% Endpoints, Am. J. Hyg. **27:**493-497 (May) 1938.

11. Hammon, W. M.: Encephalitis, in Diagnostic Procedures for Virus and Rickettsial Diseases, ed. 2, New York, American Public Health Association, 1956, pp. 197-201.

12. Fulton, F., and Dumbell, K. R.: Serological Comparison of Strains of Influenza Virus, J. Gen. Microb. **3**:97-111 (Feb.) 1949.

13. Svedmyr, A.; Enders, J. F.; and Holloway, A.: Complement Fixation with 3 Types of Poliomyelitis Viruses Propagated in Tissue Culture, Am. J. Hyg. **57**:60-70 (Jan.) 1953.

14. (*a*) Hammon, W. M.; Ludwig, E. H.; Sather, G. E.; and Schrack, W. D., Jr.: Longitudinal Study of Infection with Poliomyelitis Viruses in American Families on Philippine Military Base, During Interepidemic Period, Ann. New York Acad. Sc. **61**:979-988 (Sept.) 1955. (*b*) Hammon, W. M., and others: Problems Raised by Certain ECHO Viruses in Attempted Laboratory Detection of Poliomyelitis Virus Infection, ibid. **67**:304-310 (April 19) 1957. (*c*) Hammon, W. M.; Ludwig, E. H.; Sather, G.; and Yohn, D. S.: Comparative Studies on Patterns of Family Infections with Polioviruses and ECHO Virus Type 1 on an American Military Base in Philippines, Am. J. Pub. Health **47**:802-811 (July) 1957.

15. (*a*) Svedmyr, A., and Kjellen, L.: Discussion at VI International Congress on Microbiology, Rome, 1953. (*b*) Von Zeipel, G., and Svedmyr, A.: Study of Association of ECHO Viruses to Aseptic Meningitis, Arch. ges. Virusforschung **7**:355-368 (May) 1957. (*c*) Johnsson, T.: Discussion presented at Fourth International Poliomyelitis Conference, Geneva, 1957, to be published. (*d*) Melnick, J. L.: Isolation of Virus and Development of Neutralizing and Complement-Fixing Antibodies in Poliomyelitis Patients, Ann. New York Acad. Sc. **61**:1005-1010 (Sept.) 1955.

16. Arnold, J. H., and Enders, J. F.: Personal communication to the authors.

17. (*a*) Neva, F. A.; Feemster, R. F.; and Gorbach, I. J.: Clinical and Epidemiological Features of Unusual Epidemic Exanthem, J. A. M. A. **155**:544-548 (June 5) 1954. (*b*) Reference 1*b*.

18. (*a*) Ormsbee, R. A., and Bell, E. J.: ECHO Viruses from Idaho and Montana, Am. J. Pub. Health **47**:1405-1413 (Nov., part 1) 1957. (*b*) Wenner, H. A., and Chin, T. D. Y.: Discussion of ECHO Viruses, in Cellular Biology, Nucleic Acids and Viruses, Special Publications of New York Academy of Sciences **5**:384-387 (Dec.) 1957. (*c*) References 1*b* and 15 *c*.

19. Wehrle, P. F.; Hammon, W. M.; Coriell, L. L.; and McAllister, R. M.: Spread of Poliovirus Infection During Epidemic of Unusual Severity, Woodbury County, Iowa, and Dakota County, Nebraska, 1952, Am. J. Hyg. **65**:386-403 (May) 1957.

20. Reference 18*a* and *b*.

21. Kibrick, S., and Benirschke, K.: Acute Aseptic Myocarditis and Meningoencephalitis in Newborn Child Infected with Coxsackie Virus Group B, Type 3, New England J. Med. **255**:883-889 (Nov. 8) 1956.

22. References 1*b*, 2, 17*a*, and 18*a* and *b*.

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COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations.

H. D. KAUTZ, M.D., *Secretary.*

CURRENT STATUS OF THERAPY IN ANEMIAS

Herbert C. Lichtman, M.D., Brooklyn, N. Y.

Anemia, like any other useful sign of disease, is most efficiently corrected when therapy is directed at the specific pathological process or deranged physiological mechanism responsible for its development. The administration of a blood transfusion is the only direct treatment for anemia. It is effective in elevating the hemoglobin concentration, although often only temporarily, in a wide variety of disease states, even when it is employed without regard to the pathogenesis of the anemia. This is somewhat similar to the indication for an alcohol sponge bath for the patient with excessively high fever or the use of tracheotomy for acute laryngeal edema. All are useful, sometimes lifesaving, direct therapeutic attempts to relieve an abnormal sign of disease without altering the causative factors.

Anemia is usually defined as the state in which there is found a reduction in the concentration of hemoglobin, the number of erythrocytes, or the volume of packed red blood cells in a specific quantity of the circulating blood. The mean values for these measurements found in healthy adult males, adult females, and children of various ages differ significantly, as indicated in table 1.

No single value can be used, therefore, as a standard of reference ("100% level") for hemoglobin concentration, red blood cell count, or hematocrit for all individuals. Thus, many "slight anemias" of females are seen to be spurious when the hemoglobin values are judged in the correct frame of reference.

From the Department of Medicine, College of Medicine at New York City, State University of New York.

Since anemia is so often an early sign of disease, its presence should be established with care. The methods available for the detection of anemia include the red blood cell count, the determination of hemoglobin level, and the measurement of the volume of packed red blood cells (the hematocrit). Of the three, the enumeration of red blood cells is the least accurate and the most difficult and time-consuming to perform (table 2). It would seem, therefore, that the red blood cell count should not be used as a screening procedure for anemia but should be determined only when it is of interest to calculate the red blood cell indexes.

TABLE 1.—*Comparison of Mean Values in Clinical Examination of Blood of Children and Adults*

Age	Red Blood Cell Count, Million/Cu. Mm.	Hemoglobin, Gm./100 Ml.	Packed Red Blood Cells, Ml./100 Ml.
First day	5.1±1.0	19.5± 5.0	54.0±10.0
3-5 mo.	3.8 - 5.2	9.9 - 14.5	36.0
1-10 yr.	4.0 - 5.0	11.0 - 13.0	30 - 40
Adult female	4.8±0.6	14.0± 2.0	42.0± 5.0
Adult male	5.4±0.8	16.0± 2.0	47.0± 7.0

Anemia will develop as a consequence of increased blood loss from the body, excessive blood destruction, impaired blood cell formation, or combinations of these mechanisms (table 3). The accurate simultaneous measurement of the hemoglobin concentration, volume of packed red blood cells, and the erythrocyte count, plus a careful examination of a properly spread and stained blood film, will permit the calculation of the mean corpuscular volume, the mean corpuscular hemoglobin concentration, and the detection of unusual types of erythrocytes, such as spherocytes, schistocytes, sickle cells, target cells, stipple cells, and ovalocytes. A morphologic classification of anemias, which is of great value in diagnosis and therefore in therapy, can be constructed on the basis of the corpuscular constants and the appearance of the erythrocytes (table 4).

TABLE 2.—*Comparison of Accuracy of Three Laboratory Methods of Detecting Anemia*

Method	Minimal Error, 2 C.V., * %	Usual Error, 2 C.V., %	Usual Error Limits	True Value
Red blood cell count, million/cu. mm.	±11	±30†	3.5 - 6.5	5.00
Hemoglobin,‡ Gm./100 ml.	± 2	± 5	14.3 - 15.7	15.00
Packed red blood cells, ml./100 ml.	± 1	± 1	49.5 - 50.5	50.00

* Coefficient of variation.
† One pipet, one chamber.
‡ Photoelectric colorimeter.

Microcytic Hypochromic Anemias

For this discussion, an anemia is classified as microcytic hypochromic when the mean corpuscular volume is below 80 cu. μ and when the mean corpuscular hemoglobin concentration is below 30%. This group includes all the anemias which will respond to the administration of iron. Stated in another way, iron is an effective therapeutic agent only in this category. Iron deficiency may develop as a result of chronic blood loss in the fully grown individual or as a result of diet nutritionally inadequate for iron salts in the growing child. In both, the erythrocytes will be small and appear pale and poorly filled with hemoglobin on the stained blood film. Sometimes the microcytic hypochromic anemia may be the first sign of occult blood loss. This is especially true in the adult male who does not have the repetitive assault upon his iron reserves, as does the female, incident to gestation or menstruation. Here the finding of microcytic hypochromic anemia makes mandatory a careful scrutiny for chronic bleeding, such as the easily overlooked blood loss which results from gastrointestinal ulceration.

TABLE 3.—*Etiological Classification of Anemias*

I. Loss of Blood
  A. Acute
  B. Chronic
II. Excessive Destruction of Erythrocytes
  A. Intracorpuscular defect
  B. Extracorpuscular defect
III. Impaired Production of Erythrocytes
  A. Deficiency of substances necessary for erythropoiesis
    1. Iron
    2. Cyanocobalamin (vitamin B_{12})
    3. Folic acid
    4. Protein
    5. Ascorbic acid (vitamin C)
    6. Other vitamins
    7. Trace elements
  B. Congenital defects in erythropoiesis
    1. Abnormal hemoglobin diseases
    2. Thalassemia
    3. Congenital spherocytosis
  C. Acquired defects in erythropoiesis
    1. Infection
    2. Renal disease and other chronic disease
    3. Noxious agents, lead, irradiation, drugs
    4. Endocrine abnormalities
    5. Bone marrow replacements or infiltration
    6. Splenic disorders

Iron deficiency anemia is treated by the administration of iron in quantities that are adequate and in a form that is well tolerated and utilizable by the patient. Oral administration of ferrous salts is the preferred route in all but a small percentage of patients. This latter group, for reasons discussed later, requires parenteral administration of iron compounds.

The effective dose of iron administered is limited by the restricted capacity of the gastrointestinal tract to absorb iron. The normal individual may absorb approximately 5 to 15% of ferrous iron and 2 to 10% of ferric iron salts, when ingested in quantities up to 100 mg. per day. Above this level the fraction of iron absorbed decreases as the total amount administered is increased.

When iron deficiency exists, the percentage absorbed is probably increased considerably. The contents of the intestinal lumen also have an effect on iron absorption, i. e., the tenfold to twentyfold increase in absorption resulting from the simultaneous administration of ascorbic acid or the decrease in the availability of iron for absorption when insoluble salts are formed with phosphates or other compounds.

In general, an inorganic salt of iron in the reduced form, such as ferrous sulfate, is perfectly adequate for the treatment of iron deficiency anemia. It may be administered orally in a dosage of about 1 Gm. per day and will supply about 200 mg. of elemental iron, of which at least 20 mg. will be absorbed. A schedule such as 330 mg. of ferrous sulfate given after each meal, with 50 to 100 mg. of ascorbic acid, is frequently employed. There seems to be no advantage to the addition of cobalt, copper, molybdenum, intrinsic factor, cyanocobalamin (Berubigen, Bevatine, Bevidox, Bexii, Cobione, Dodecabee, Dodex, Hemomin, Rametin, Redisol, Rubramin, Sytobex, Vibalt, Vitamin B_{12}), folic acid (Folic Acid, Folvite), or other vitamins or trace metals. The higher cost of "shotgun" preparations and the smaller dose of elemental iron usually supplied with such mixtures actually are disadvantageous.

Gastric irritation, diarrhea, and/or constipation, which develop in some patients receiving iron therapy, are often avoided by the administration of smaller doses at the onset of therapy with a gradual increase to full dosage within a period of a week or two. Occasionally, ferrous gluconate, ferrous carbonate, or ferric ammonium citrate may be found less irritating than ferrous sulfate and better tolerated by specific patients. However, larger total daily dosages are required of these salts in order to supply equivalent quantities of elemental iron.

For infants to whom solid medication cannot be administered, iron ammonium citrate in water and glycerin is employed at dosages of about 200 mg. three times each day. When the infant is about one year old, two or three times this dose is given. An elixir of ferrous sulfate (to prevent oxidation to ferric form), with the following ingredients and amounts, is often employed: 0.6 cc. of dilute hypophosphorus acid, 3 Gm. of ferrous sulfate, 30 Gm. of dextrose, and chloroform water, N. F., to make 120 cc. A dose of 4 cc. is given three times daily after meals.

When oral administration in any form is impractical in the infant, the intramuscular injection of iron, as in the form of an iron-dextran complex (Imferon), is of real value. One cubic centimeter of this preparation contains 50 mg. of elemental iron which, when injected deep into the muscle, is freely available to the iron pool of the body. Its administration has been free of adverse side-reactions and can be recommended in all instances when the oral route of iron administration is ineffective or impractical. When given parenterally, the total dose of iron administered should be calculated with care. Since practically no iron is lost from the body once it enters the tissues, except through blood loss, the parenteral administration of great excesses of iron over long periods of time will lead to tremendous iron concentrations in the body and conceivably diffuse tissue injury (i. e., exogenous hemochromatosis).

TABLE 4.—*Morphologic Classification of Anemias*

Index	Method for Calculation	Normal	Macrocytic	Microcytic	Hypochromic
Mean corpuscular volume, cu. μ	$\frac{\text{hematocrit} \times 10}{\text{red blood cells (million/cu. mm.)}}$	82-92	Above 94	Below 80	...
Mean corpuscular hemoglobin concentration, %	$\frac{\text{hemoglobin (Gm./100 ml.)} \times 100}{\text{hematocrit}}$	32-36	...	...	Below 30

The dose of iron employed depends on the deficit in total body hemoglobin, which can be calculated from the body weight and peripheral blood hemoglobin concentration. For example, in an infant one year of age weighing 9 kg. (20 lb.), the hemoglobin concentration is found to be 6 Gm. per 100 ml. of blood. If one considers a hemoglobin level of 13.0 Gm. per 100 ml. of blood to be normal at this age, a deficit of 7 Gm. per 100 ml. of blood exists. The blood volume at this age may be expected to be 80 ml. per kilogram of body weight or 720 ml. in this instance. The total body hemoglobin deficit is found to be $\frac{7 \text{ Gm.} \times 720 \text{ ml.}}{100 \text{ ml.}}$ or 50.4 Gm. Since each gram of hemoglobin utilizes 3.4 mg. of iron, 50.4 × 3.4 or 171.4 mg. of iron is required to restore the hemoglobin level to normal. An additional 20% is usually given in order to reconstitute the iron stores of the body. This would increase the dose to approximately 200 mg. of iron, which can be administered intramuscularly in 1-cc. injections (50 mg. per cubic centimeter) daily for four days. Simple charts, which are based on calculations similar to these, are available for the determination of the correct dose of iron given par-

enterally. They relate total dose of iron to the weight of the patient and his initial hemoglobin concentration.

Saccharated iron oxide (Proferrin) is another form of iron available for parenteral use. This is given intravenously, diluted in saline solution, at doses of 50 to 100 mg. per injection, to adults. Smaller amounts are recommended for children. Since its wide use during the past several years, it has been demonstrated to be more effective and far less toxic than earlier intravenously administered iron preparations had been. However, as with all forms of iron given parenterally, a regular incidence of toxicity occurs which requires one to exercise extreme care with each administration. Perhaps more important is the necessity for a compelling indication for the use of this form of therapy as opposed to oral treatment. These indications in an adult include a malabsorption syndrome, making oral therapy with iron preparations ineffective, and extreme sensitivity of the gastrointestinal tract to iron salts because of intrinsic disease or idiosyncrasy.

TABLE 5.—*Disorders Associated with Megaloblastic Anemia*

Disease	Effective Therapeutic Agents
Pernicious anemia	Cyanocobalamin
Nutritional macrocytic anemia	Cyanocobalamin in some cases and folic acid in others
Sprue, idiopathic steatorrhea	Cyanocobalamin and/or folic acid
Total gastrectomy	Cyanocobalamin
Intestinal strictures, blind loops	Surgical correction, broad-spectrum antibiotics, cyanocobalamin, folic acid
Diphyllobothrium latum infestation	Cyanocobalamin
Megaloblastic anemia of infancy	Folic acid, ascorbic acid
Megaloblastic anemia of pregnancy	Folic acid
Tropical macrocytic anemia	Folic acid and/or cyanocobalamin
Achrestic anemia	Folic acid

Another cause of microcytic hypochromic anemia is thalassemia. In this hereditary disorder there exists a congenital defect in erythropoiesis. Inadequate numbers of red blood cells are produced, and those that are found are abnormal. They vary a great deal in size and shape; many target cells and small fragmented erythrocytes (schistocytes) are seen as well as normoblasts and stipple cells. Since the survival time of these cells in the circulation is shortened, two factors are present to account for the anemia: inadequate production and excessive hemolysis. At times, there occurs in these patients the complicating factor of an extracorpuscular hemolytic state which offers an additional therapeutic challenge. In this disease, in spite of the resemblance to iron deficiency anemia, administered iron is not beneficial and actually may be harmful. Iron stores are usually excessive. It is the utilization of the available iron which seems to be disturbed.

The treatment for thalassemia is symptomatic. Transfusions are administered when the hemoglobin level falls below a critical point at which symptoms of anemia become manifest. Although this varies widely in individual children with this disease, in general, a hemoglobin value of less than 7.0 Gm. per 100 ml. of blood is the usual indication for transfusion. It is not practical to attempt to maintain the hemoglobin at normal levels by transfusion and actually is harmful. Not only is the risk of transfusion reaction and serum hepatitis increased, but the large numbers of transfusions required only seem to speed up the development of hemosiderosis and finally of hemochromatosis, which develops eventually in patients with thalassemia major and which is the ultimate cause of death in many of these children. In selected instances, splenectomy has been found to be effective in thalassemia when an extracorpuscular hemolytic anemia exists.

Macrocytic Anemias

For this discussion, an anemia is classified as macrocytic when the mean corpuscular volume is greater than 94 cu. μ. These anemias can be divided into two large groups: (1) those associated with megaloblastic erythroid precursors in the bone marrow and (2) those associated with normoblastic erythroid precursors. The megaloblastic anemias form a large group of entities with the following common characteristics: macrocytic normochromic erythrocytes, megaloblastic erythropoiesis, leukopenia, thrombocytopenia, and dramatic therapeutic response to specific antianemic preparations. Depending upon the pathogenesis of the disorder, such preparations include cyanocobalamin, folic acid, and ascorbic acid.

Pernicious anemia and related disorders are usually readily diagnosable when patients are seen in hematological relapse. A diagnosis of pernicious anemia, sprue, and megaloblastic anemia incident to total gastrectomy demands therapy for the remainder of the life of the patient. A definitive diagnosis therefore should be established before therapy is undertaken, since partial remission induced by suboptimal therapy can make the diagnosis difficult to establish. Table 5 includes a list of the different disorders often associated with megaloblastic anemia and the usually effective therapeutic agents.

Pernicious Anemia.—For patients in relapse, cyanocobalamin is the drug of choice in this disease. It is administered intramuscularly in doses of about 30 mcg. daily until a good hematological response is observed, usually for about two weeks. If the number of reticulocytes has not risen within the first 10 days, the correctness of the diagnosis should be suspected. Within two weeks the hemo-

globin level, hematocrit, and red blood cell values should rise considerably. The percentage of increase is usually proportional to the severity of the anemia prior to therapy; that is, greater gains will be made in the more anemic patients. After two weeks the dose may be reduced to 30 mcg. given once or twice per week. Maintenance therapy is required for the life of the patient and may be adequately carried out with 45 to 60 mcg. of cyanocobalamin injected intramuscularly at intervals of four to six weeks. When severe combined systemic disease (posterolateral sclerosis) is found, it is recommended that a larger dose of cyanocobalamin be given at more frequent intervals.

Liver extract is equally effective in pernicious anemia when administered in comparable dosage; i. e., one unit of liver extract is equivalent to one microgram of cyanocobalamin. There is no real evidence that liver extract has any more value in this disease than can be accounted for by its cyanocobalamin content. Since it is more painful to inject, allergic reactions do occur in some patients; and since larger volumes are required for comparable cyanocobalamin content, it is not as desirable as cyanocobalamin.

Oral administration of cyanocobalamin alone is ineffective, because the basic defect in pernicious anemia is the absence of gastric intrinsic factor required for its absorption. Exceptionally large oral doses (3,000 mcg.) are capable of inducing remission, but the expense of this form of therapy precludes its use.

Cyanocobalamin, combined with potent intrinsic factor from animal sources, can be used orally to induce remission and can maintain patients in good health for long periods. This form of therapy is not yet considered as reliable as parenteral therapy with cyanocobalamin alone because of a wide variation in the potency of various intrinsic factor concentrates and because of the uncertainty of the stability of some of these preparations when stored. For these reasons, at this time such therapy is not considered suitable for routine use.

Folic acid is contraindicated in pernicious anemia, and iron is required only when a combined iron deficiency exists. However, folic acid is indicated for the treatment of megaloblastic anemia of pregnancy, megaloblastic anemia of infancy, some cases of sprue, nutritional megaloblastic anemia, tropical macrocytic anemia, and refractory megaloblastic anemia. The usual dose is 5 to 20 mg. daily, administered orally. Parenterally administered preparations, such as sodium folate (Sodium Folvite), are available for use in infants or in adults too ill to tolerate oral therapy. In the megaloblastic anemias of infancy and pregnancy, therapy is usually indicated until hematological remission is induced, and then it may be stopped without relapse occurring. In sprue and nutritional megaloblastic anemias, the administration of folic acid may be required for long periods and sometimes indefinitely.

Macrocytic Anemias Without Megaloblastosis

Macrocytic anemias without megaloblastosis form a heterogeneous collection of disorders usually secondary to some primary disease not localized to the hematopoietic system. In chronic liver disease, which is the most common cause, the erythrocytes are large and often very thin so that increased numbers of target cells are seen. Chronic blood loss is frequent in cirrhosis of the liver, probably as a result of bleeding from esophageal varices, hemorrhoids, or peptic ulcerations. As a result, macrocytic hypochromic cells are found. Iron therapy will partially influence the hemoglobin values beneficially. The underlying liver failure is in some way responsible for most of the hemoglobin deficit, however, and this is refractory to therapy directly with any of the known hematinics.

Scurvy.—When scurvy is severe enough, it may be associated with a macrocytic anemia reputedly, in some instances, associated with megaloblastic erythropoiesis. Ascorbic acid is the specific agent in the treatment of this disorder. In this instance, leucovorin (citrovorum factor) theoretically may have a specific role in the treatment of anemia, since ascorbic acid depletion is associated with a decrease in the conversion rate of folic acid to citrovorum factor.

Anemia of Myxedema.—In the endocrine deficiency, myxedema, anemia is frequently found. The erythrocytes may be microcytic hypochromic (probably when associated with menorrhagia in females), normocytic normochromic, or macrocytic. The use of thyroid or its active principles for the treatment of the underlying hypothyroidism is frequently effective in restoring blood values to normal. Iron may be required in the depleted individual.

Normochromic Normocytic Anemias.—For this discussion, an anemia is classified as normocytic normochromic when the mean corpuscular volume is 82 to 92 cu. μ and the mean corpuscular hemoglobin concentration is 32 to 36%. The anemias found in this morphologic category include almost all types of anemia not already discussed.

Acute Blood Loss.—When severe hemorrhage occurs, the degree of anemia, as depicted in the peripheral blood cell counts at any one moment, is dependent upon a variety of factors. Some of these include (1) the amount of whole blood lost, (2) the original size of the vascular space, (3) the alterations which have occurred in the size of the

vascular compartment, i. e., vascular contraction or expansion, (4) the amount of plasma or red blood cell regeneration, and (5) shifts in the intravascular localization of blood from one area to another, i. e., splanchnic pooling or peripheral vasoconstriction.

The hemoglobin concentration or the volume of packed red blood cells obtained from a sample of peripheral blood, therefore, will not necessarily directly reflect the total amount of blood loss. Immediately after a hemorrhage the blood values may be normal. As plasma is replaced into the vascular space, even though bleeding has ceased, the values will progressively fall for as long as 12 to 24 hours. If circulatory collapse occurs, hemoconcentration may occur, and blood cell counts may rise.

Therapy for hemorrhage includes transfusion of whole blood to replace the volume lost and measures directed at correcting the bleeding. There is no substitute equal to whole blood transfusion for the treatment of hemorrhage. Normal human plasma is used only when blood is not available, as a temporary measure to maintain circulating volume. Ideally the transfused blood should be antigenically similar to that of the recipient in regard to major group and Rh type. Crossmatching should always be performed to eliminate the possibilities of incompatibilities not detected otherwise. For the patient who has had transfusions previously, the extra precaution of employing the indirect Coombs crossmatching method is considered worth the additional effort. Even when relatively mild, the reaction which follows in the wake of an incompatible transfusion can be disastrous for the patient who is under the physiological stress of acute hemorrhage.

Hemolytic Anemias.—Although each of the many types of hemolytic anemia occurs infrequently, the category, as a whole, is a sizable one. It is beyond the scope of this presentation to review the pathogenesis and therapy for each of the disease states associated with an excessive rate of erythrocyte destruction. Some generalizations are possible, however. All the hemolytic anemias may be considered to fall into two groups: those associated with an abnormality intrinsic in the erythrocyte as it is developed (intracorpuscular defect) and those in which the primary defect is an abnormality present in the environment of the erythrocyte, which then alters the viability of the normally produced cell (extracorpuscular defect).

The four basic measures employed in the management of hemolytic anemias include (1) administration of corticotropin (Acthar, Corticotropin, Depo-Acth) or adrenal cortical steroids, (2) splenectomy, (3) transfusion, and (4) removal of any adverse environmental factors.

Adrenal Steroid Therapy: Adrenal steroid therapy, as typified by the administration of corticotropin, cortisone (Cortisone, Cortogen, Cortone) acetate, and prednisone (Deltasone, Deltra, Meticorten), is of great value in the management of the extracorpuscular hemolytic anemias. The types most often benefited include the idiopathic, acquired hemolytic anemias with and without demonstrable antibodies, the symptomatic hemolytic anemias (those associated with malignant lymphomas, chronic lymphocytic leukemia, collagen diseases, and miscellaneous tumors), and the hemolytic states resulting from drug sensitivities. The dosage of corticotropin usually employed is 25 to 50 U. S. P. units given intramuscularly every six hours. It may be used intravenously as well. A dosage of 25 to 50 units of corticotropin, dissolved in a liter of isotonic sodium chloride solution and administered by slow drip over a period of 16 to 20 hours, may produce a rapid therapeutic response. Cortisone, in quantities up to 300 mg. per day, or prednisone, in amounts up to 100 mg. per day, is occasionally required to halt the hemolytic process in refractory cases. Usually less is required. When a response is noted, that is, when hemoglobin values rise and the indications of hemolysis disappear, the steroid dosage may be decreased slowly. A gradual weaning process is often necessary in the patient receiving adrenal steroids. The patient should be carefully observed for recurrence of hemolysis when low levels of medication are reached. Often, prolonged maintenance therapy is required at a daily dose level which varies with each patient but which should be just adequate to prevent hemolysis.

Splenectomy: Splenectomy is resorted to in patients with acquired hemolytic anemias when adrenal cortical steroids either prove ineffective or are contraindicated for some reason. In patients with hereditary spherocytosis with anemia, it is the treatment of choice. In this disorder, the hemolytic anemia is uniformly benefited, although the basic intracorpuscular defect persists. In the uncomplicated case of thalassemia or sickle cell disease, splenectomy is of no benefit. However, there are certain instances of these diseases in which transfusion requirements are excessive and in which an extracorpuscular hemolytic mechanism, which is superimposed upon the basic disease, can be demonstrated. It is only in these patients with thalassemia and sickle cell anemia that splenectomy may be beneficial.

Transfusions: Transfusions are administered to all patients with hemolytic anemia when the number of circulating erythrocytes falls to very low levels. Usually an absolute indication for blood transfusion is the finding of the hemoglobin concen-

tration below 7.0 Gm. per 100 ml. Coronary artery disease, myocardial failure, or rapid hemolytic rates may require the use of transfusion sooner. Great caution must be exercised when administering a transfusion to patients with acquired hemolytic anemia who have autoantibodies. Occasionally, panagglutinins are present which make proper crossmatching and typing of blood extremely difficult. At times the transfusion of packed red blood cells or saline-washed erythrocytes reduces the incidence of reactions.

Removal of Adverse Environmental Factors: The removal of adverse environmental factors is the fourth measure employed in the treatment of hemolytic anemia. This refers particularly to the acquired hemolytic anemias when the pathogenesis is known. The chemotherapy of malaria or the antibiotic treatment of septicemia is, of course, the method of choice in the treatment of the hemolytic anemias associated with these diseases. It is of value to remember that the presenting sign of a disease such as subacute bacterial endocarditis may be hemolytic anemia. When a chemical agent can be implicated in the pathogenesis of hemolytic anemia, its removal from the internal or the external environment of the patient may be all that is necessary to effect a cure. Industrial exposure to naphthalene, trinitrotoluene, benzene, nitrobenzene, aniline, lead, and methyl chloride and medicinal exposure to sulfonamides, quinine, pamaquine, primaquine, and aminosalicylic acid (*p*-Aminosalicylic Acid, Pamisyl, Para-Aminosalicylic Acid, Para-Pas, Parasal, Propasa) have been implicated not infrequently in the production of hemolytic anemia. A complete medical history, taken with especial emphasis on any such industrial, household, or pharmacological exposure, is often the most important potentially therapeutic step that can be taken by the attending physician. There is no evidence to suggest that cyanocobalamin, liver extract, folic acid, or any other vitamins have any specific therapeutic benefit in the management of hemolytic anemia. Iron is not necessary, since the iron liberated by the hemolyzed erythrocytes is not lost from the body and is readily available for new hemoglobin production. The one exception to this is in the management of patients with hemolytic anemia associated with chronic hemoglobinuria, such as paroxysmal nocturnal hemoglobinuria. In this disorder, enough hemoglobin and its associated iron may be lost in the urine to necessitate supplementation with iron salts.

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Anemias Due to Bone Marrow Hypofunction

For this discussion, an anemia due to bone marrow hypofunction is a disorder in which the red blood cells are usually normochromic and normocytic. The causes for bone marrow hypofunction can be considered in five groups: (1) chemical or physical injury of marrow, (2) invasion of marrow by nonhematopoietic cells, (3) metabolic interference with erythropoiesis, (4) hormonal factors, and (5) idiopathic hypofunction (table 6).

Except for the use of splenectomy in hypersplenism and hormonal replacement in endocrine deficiency states, no specific treatment exists for the anemia present in this collection of disorders. When an underlying disease such as chronic infection or lymphoma is responsive to direct therapeutic measures, the anemia will respond simultaneously. Supportive measures such as transfusion have value in the severely anemic person. A dose of 50 mg. of cobalt chloride daily has been used with some success. Although its exact mode of action is unknown, cobalt seems to behave as a stimulant to erythropoiesis. It is potentially toxic and is often poorly tolerated, causing nausea and diarrhea. Although some rise in red blood cell counts may follow its administration, subjective deterioration is frequent and its use has to be abandoned. The known hematinics such as iron, folic acid, cyanocobalamin, and liver extract have no value in this group of diseases.

TABLE 6.—*Anemias Due to Bone Marrow Hypofunction*

Chemical or Physical Injury to Marrow	
Irradiation	Heavy metals
Radioactive substances	Sulfonamides
Nitrogen mustards	Chloramphenicol
Thiourea compounds	Phenylbutazone
Benzene	
Myelophthisis Due to Presence of Abnormal Tissue in Marrow	
Metastatic neoplasms	Lipoidosis
Multiple myeloma	Osteosclerosis
Lymphoma	Myelofibrosis
Leukemia	
Metabolic Inhibition	
Uremia	Chronic liver disease
Infection	Malignancy
Hormonal Factors	
Hypersplenism	Hypothyroidism
Hypopituitarism	
Idiopathic Hypofunction	
Refractory anemia	Aplastic anemia

Summary

Anemia is not a disease but a designation given to a laboratory finding present in almost all chronically ill patients and in many whose illness is of short duration. When possible, therapy is directed at the underlying disease. This implies the necessity for a precise diagnosis. Often, careful analysis of the blood by the judicious use of clinical laboratory methods is of great assistance in arriving at a diagnosis and thereby the selection of effective therapeutic agents.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
Edited Under the Direction of the Board of Trustees

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Subscription price . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

NUTRITION AND MEDICAL PROBLEMS

THE chemical composition of any food, drug, or poison taken into the body can have a profound effect on one's body, mind, and spirit. Heretofore nutritionists have been chiefly concerned with determining the chemical composition of the foods most commonly used, with little thought for their relation to medical problems. No one has been more active in bringing this relationship to both nutritionist and physician than has Dr. Spies, whose latest contribution to this field appears in this issue (page 675). As in almost any field, what at first appeared simple is found with each new discovery to be anything but simple. Although research rarely does and is not expected to give us definitive answers to all questions, every advance in our knowledge of nutrition should when properly applied aid in building health and preventing disease. Many diseases formerly of unknown origin are now recognized as due wholly or in part to chemical imbalances within the body.

In any effort to prevent disease early recognition is an important factor. Diagnostic criteria originally based on descriptions of far-advanced cases of such diseases as pellagra and sprue are of little or no value in early recognition, and when recognition of the cause of a disease leads to prevention the advanced cases become a rarity. This necessitates setting up new criteria for finding the early and the chronic but mild cases—always a more difficult problem. Meanwhile many such cases go unrecognized, misdiagnosed, and improperly treated. It is difficult to think of a more frustrating experience for such a patient than to go on for years labeled a hopeless neurotic. These patients can never get well on placebos or bromides, but when the deficient element in the diet is supplied they promptly regain their health.

Another important point to remember is that apparently no one develops a deficiency of only one of the water-soluble vitamins. It seems to be necessary when such a deficiency is discovered to search for others and correct them. Unlike smallpox, one attack of a nutritional deficiency does not confer immunity. The only prevention is a daily supply of all the necessary elements in the diet. Of course no one should get the impression that all diseases are caused by a nutritional deficiency or can be prevented by an adequate diet. The important thing to remember is that chemical imbalances in the body may play a part in any disease and do play a large part in many a condition in which the possibility of nutritional deficiency is not even considered.

REGISTRATION UNDER THE HARRISON NARCOTIC ACT

Physicians who are registered under the Harrison Narcotic Act or under the Marihuana Tax Act must effect reregistration on or before July 1 to avoid penalty. Each year, despite the annual warnings in THE JOURNAL, this requirement is overlooked by some physicians, and unpleasant consequences follow.

Failure to register adds a penalty of up to 25% to the tax payable and, in addition, subjects the physician who continues to dispense to the possibility of a fine not exceeding $2,000 or imprisonment for a maximum of five years, or both. The Commissioner of Internal Revenue has in past years given some tardy registrants the choice of paying sums by way of compromise, a procedure authorized by law, or accepting criminal prosecution. If this procedure does not produce the required promptness in reregistration, the commissioner will have no choice but to institute criminal prosecution.

This requirement for registration and reregistration does not apply to the physician who does not intend to prescribe or use narcotics in his practice or to possess narcotics.

ORGANIZATION SECTION

THE FORAND BILL

Recently there was issued from the American Medical Association a booklet entitled "Facts About the Forand Bill." This booklet lists 15 questions with answers. In addition, Dr. David B. Allman, President of the American Medical Association, on April 4, mailed to members of the A. M. A. a letter in which he commented on the Forand Bill HR 9647. Since then, Aime J. Forand has written to Dr. F. J. L. Blasingame, commenting on the A. M. A. leaflet and Dr. Allman's letter. For the readers of THE JOURNAL, *the leaflet, Dr. Allman's letter, and Representative Forand's letter are reproduced.*—ED.

Facts About the Forand Bill

1. Q. *What is the Forand bill?*

A. The Forand bill, H. R. 9467, is an AFL-CIO sponsored amendment to the present Social Security Act. The bill proposes to provide government hospital and surgical care for approximately 13 million eligible social security claimants, principally persons over 65. The bill was introduced in the House in August 1957 by Rep. Aime J. Forand (D., Rhode Island). It was referred to the House Ways and Means Committee of which Forand is the third ranking member. The committee is expected to begin hearings in May.

2. Q. *In brief, what would the Forand bill do in the field of health care?*

A. Bring the aged and other Old-Age Survivors Insurance claimants under government-supervised health care. The government would make contractual agreements to reimburse hospitals, nursing homes, physicians and dentists for specified services rendered to the 13 million (1958) social security claimants (expected to be as many as 22 million by 1975). Payments would be made directly to hospitals, physicians and nursing homes. No payments would be made to individual claimants.

3. Q. *What would the health care proposals cost all workers?*

A. There is no way of accurately predicting the cost. It could prove so costly that it would jeopardize the retirement security of millions of Americans who depend on social security for their basic retirement needs. For the first time last year the social security system received less income than it paid out. Taxes to finance the present program are already scheduled to reach 8½% of payroll up to $4,200 in coming years. The Forand bill provides for raising the social security tax base from the first $4,200 of income to the first $6,000. The tax rate would also be increased ½ of 1% for both employers and employees and ¾ of 1% for self-employed persons. This increase, in addition to those already provided by the social security law, would mean that a self-employed person could be paying $427.50 in social security taxes by 1975.

4. Q. *Would this raise in the social security tax cover the cost of the program?*

A. Possibly at its inception. However, other countries with similar socialistic health programs have found that their costs were several times larger than the original estimates. It is most likely that the Forand bill program would eventually cost much more than two billion dollars per year and that the taxes woud have to be raised accordingly.

5. Q. *What are the basic faults of the Forand bill in the field of health care?*

A. The Forand bill proposes a political solution to a health problem. It is a health care bill developed by non-medical people (chiefly the AFL-CIO).

6. Q. *Would the Forand bill adversely affect health care for the rest of the population?*

A. Over-utilization of hospitals by social security claimants would limit the number of beds available for the acutely ill of all ages in the community. Provisions for extensive free hospitalization would create needless and dangerous crowding of hospital space. In many countries where similar legislation is in effect, there has been a staggering increase in use of hospital facilities by those over 65. (In Saskatchewan, Canada, for example, the average person over 65 occupies a hospital bed 7.2 days a year; in the United States the average person over 65 occupies a hospital bed 2.5 days a year.)

7. Q. *Could all doctors, hospitals and nursing homes participate?*

A. No. Only those that enter into contracts with the government. Furthermore, except in an emergency, surgery could be performed only by a surgeon certified by the American Board of Surgery or one who is a member of the American College of Surgeons. Elective surgery is not included. Care would not be authorized in a mental or tuberculosis hospital. Nursing homes would (1) have to be operated in connection with a hospital or (2) operated under the general direction of a licensed doctor or surgeon.

8. Q. *Who would determine fees for doctors and charges for hospitals and nursing homes?*

A. The Federal Department of Health, Education and Welfare would make the final determination.

9. Q. *Who would administer this program and set standards of care?*

A. The program would be administered by the Secretary of Health, Education and Welfare. The government would set and enforce standards of health care under bureaucratic control.

10. Q. *What hospital and nursing home services would be provided by the Forand bill?*

A. The bill provides a combined total of 120 days free hospital and nursing home care but with a maximum of 60 days hospitalization. However, before a person can receive nursing home care he must be transferred there from a hospital for further treatment of the same illness.

11. Q. *Are any other services provided by the Forand bill?*

A. Oral surgery would be provided, but only to those persons who were hospital bed patients. Oral surgery is not defined.

12. Q. *What effect would the Forand bill have on voluntary health insurance?*

A. The health insurance industry has proved its ability to handle the extensive insurance needs of our growing population. Because of its experience and success in other fields, it is reasonable to allow it time to solve this additional problem—medical coverage for our citizens in the 65-and-over group. Approximately 50% in this age bracket has some coverage now, as compared to only 20% in 1950. Passage of the bill would give voluntary health insurance a set-back from which it would never recover. This bill would do irreparable harm to the one method through which our older citizens can take care of their health needs on a free-choice basis, maintaining full independence. Under the Forand bill the aged would become, in effect, wards of a bureaucratic system.

13. Q. *How do the uninsurable receive health care?*

A. The 3.5 million or so, 65 or over, who are uninsurable because of inadequate income, assets, or other means of support generally receive medical care through welfare programs. Aside from aid granted by many private, fraternal, and religious organizations, over three billion dollars in federal and state aid is given annually to those in the four categorical aid programs (aid to the blind, handicapped, dependent children, aged) for medical and other expenses.

14. Q. *How good are the statistics on the health problems of the aged?*

A. AMA has studied the available statistics. They have been found to be neither conclusive nor complete. The greatest need right now is for a comprehensive study of the health problems of the aged, rather than for drastic remedies for a situation about which so little is known.

15. Q. *Could the age limit for Forand health care be held at 65?*

A. Probably not. Supporters of the bill have indicated that they would like to see government-regulated health care made available to younger persons, perhaps first starting at age 60, then 55, and so on, eventually bringing everyone under a government dictated health program. Ultimately the practice of medicine in America would be totally socialized, which could result in an inferior grade of health care.

American Medical Association
April 4, 1958

Dear Doctor:

A bill now in Congress would place the health care of the aged and other OASI claimants under government supervision.

The Forand bill—H. R. 9467—would provide government hospital and medical care for about 13 million social security claimants by amending the Social Security Act. The AFL-CIO sponsored this bill and has given it top legislative priority.

The Forand bill is not in the public interest. There are several basic reasons why it is bad legislation for all Americans. These are:

1. It would bring the aged under government controlled and supervised health care. The government would set and enforce standards of health care under bureaucratic control, limiting the choice of hospitals and physicians.

2. It would eventually destroy private health insurance and the Blue Shield-Blue Cross plans.

3. It would introduce into the economy of the country, on a permanent basis, wage, fee and price fixing by government fiat.

4. It is national compulsory health insurance for a segment of our population. Once established, this concept would be extended to all social security claimants. Ultimately America would have nationalized hospitals and medical care for everyone.

5. It is an attempt to solve a complicated health problem by political means rather than through established medical resources. Making the aged wards of the government with health care handouts is not the proper way to solve the problem.

6. It would mean higher taxes and less take-home pay for all wage earners for the benefit of a minority.

7. It could bankrupt the entire social security program and jeopardize the basic retirement incomes of millions of Americans.

Every physician must be prepared to oppose this bill vigorously and be ready to make his views known to the Congress should that become necessary.

So that you may be acquainted with this ill-conceived piece of legislation, the A. M. A. has prepared the enclosed pamphlet.

Meanwhile, some of the most important and respected organizations in the health field are preparing a program which will lead toward solution of the problems of health care for the aged. Announcement of this constructive plan will be made soon and details of the program will be supplied to you.

Your active support may be needed for legislative activities which will be carried out by state and county medical societies as required by developments in the Congress.

Sincerely,
David B. Allman, M.D., President
American Medical Association

May 6, 1958

Doctor F. J. L. Blasingame
General Manager
American Medical Association
535 North Dearborn Street
Chicago 10, Illinois

Dear Doctor Blasingame:

In discussing my bill on financing health care for the aged, I have repeatedly indicated my desire to receive constructive proposals and criticisms from the medical profession. I wish very much that a plan could be developed that would be satisfactory both to doctors and to the large numbers of people who want better methods of paying for medical care for our aged citizens.

In the hope of supplying aid in securing agreement, I want to present to the readers of THE JOURNAL of the American Medical Association a few facts and explanations which will counteract false impressions likely to arise from the A. M. A. leaflet, "Facts About the Forand Bill," and from Dr. Allman's letter of April 4 to A. M. A. members.

1. The proposal embodied in my bill deals with the financing of health care, not with the nature of that care. It would no more affect the relationships between doctors, hospitals and patients than does private insurance. Specific safeguards are included against government interference with methods of medical practice.

2. As to the extent of existing health insurance among the aged: a U. S. Public Health Service Survey shows that only 36.5% of the aged, (not 50% as stated) had some form of health insurance in September, 1956. Of those thus counted as "covered," however, a large proportion had health insurance that was inadequate in scope, amount, and dependability. The necessary costs of private insurance continue to keep adequate insurance beyond the reach of the majority of aged persons and accentuate the financial problems of physicians, hospitals and welfare agencies that have to care for them when ill.

3. Instead of "destroying" voluntary health insurance as the leaflet states, my proposal would relieve insurance companies, Blue Cross, Blue Shield and the hospitals of financial responsibility for a high-cost segment of the population.

4. Far from being "socialistic," H. R. 9467 would enable people to be assured of essential care through contributions they have themselves made, rather than reluctantly be compelled to seek direct government subsidy through relief programs on a means-test basis.

5. Doctors would continue to be responsible for determining when patients should be hospitalized, the nature of their care, and the length of their stay. Problems of unnecessary hospitalization and surgery already exist under private insurance and will continue to require whatever constructive action doctors and hospitals can develop. While the bill would increase the effective demand for care, the use of nursing homes would be encouraged by my bill as an alternative to hospitalization, at lower cost.

6. Careful cost estimates have been developed in the Department of Health, Education and Welfare based on U. S. experience, including also an analysis of the very different situation in Saskatchewan. Such estimates and other official statements readily available from the Social Security Administration will show that there is no reason for fears that my proposal would cost so much as to "jeopardize the retirement of millions of Americans."

7. The A. M. A. leaflet does not mention that my bill would also raise the monthly cash payments to beneficiaries of old-age, survivors and disability insurance. The higher tax rates which the leaflet quotes are planned to cover both the costs of this average 10% increase and also the health benefits.

Sincerely yours,
AIME J. FORAND, M. C.

Representative Aime J. Forand of the 1st District in Rhode Island is Chairman of the Subcommittee on Technical and Administrative Problems on Excise Taxes and is a member of the Ways and Means Committee, Democratic Steering Committee, and the Democratic Committee on Committees.

THE MEDICARE PROGRAM

April 25, 1958

The Honorable George H. Mahon, Chairman
Subcommittee on Department of
Defense Appropriations
House of Representatives
Washington, D. C.

Dear Mr. Mahon:

I am taking the liberty of writing you because of certain questions which I understand have been raised before your Subcommittee with respect to the "free choice" provision of the legislation enacted by Congress in 1956 authorizing medical care and hospitalization for dependents of service personnel.

The questions deal in part with the economy which would allegedly result by eliminating in some instances free choice by eligible dependents between private and service physicians and facilities. The American Medical Association does not agree that tax money would necessarily be saved if dependents of service personnel are denied a free choice. Furthermore, we are convinced that elimination of free choice would result in lessening the amount of authorized medical care now available to and received by the dependents.

It is difficult for many reasons to make an accurate cost comparison between civilian and military medical care and hospitalization. Depreciation

costs, fringe benefits, as well as the expenses involved in recruitment, training, etc., are not included in computing the cost of military medical care. In this connection, we would respectfully invite your attention to the statement of Dr. Hugh Hussey before the Senate Subcommittee on Defense Appropriations on June 19, 1957. In addition, any attempt at a comparison of costs must also take into consideration the types of cases involved. The Medicare program under Title II of P. L. 569, 84th Congress, has dealt predominantly with obstetrical cases which have a relatively high cost per hospital day.

The interchange in status between eligibility and non-eligibility for civilian care would most certainly compound administrative problems. This would make DD Forms 1173 meaningless with resulting confusion among not only the dependents but civilian physicians and hospitals as well.

Many of the costs to date in the administration of P. L. 569 have been of a non-recurring nature and were necessary in contracting for civilian care through the medical associations, hospitals and their designated fiscal agencies. A significant part of this cost was for informing all parties and agencies concerned. Any change at this time would only entail further disruption in administrative mechanisms and would result in the total loss of the non-recurring expenses of inaugurating the program.

To eliminate the free choice provision in the law, as spelled out in the "implementing directives," would necessitate in many instances the exclusive utilization of military and naval facilities staffed by physicians in the uniformed services. Should this occur, and should the armed services take over the civilian phase of Medicare, or a substantial part of it, an increased demand for physicians in uniform would also undoubtedly result—a demand which could probably be met only by reactivation of discriminatory draft legislation.

In any thorough consideration of the program, it should be emphasized that dependents of those in the uniformed services are civilians and should seek their medical treatment through civilian channels if we are to preserve the beneficial aspects of our present system of providing medical care and to guard against further maldistribution of professional health personnel.

The Medicare program has been accepted by dependents of service personnel and by the medical profession and it is our understanding that it has been successful. We have also been advised that it has been economically and wisely administered. It is, therefore, our sincere recommendation that no major change affecting choice between civilian and military facilities be made in the Medicare program at this time.

Sincerely,
F. J. L. Blasingame, M.D.
General Manager

COMMITTEES ON AGING

April 30, 1958

The Honorable Roy W. Wier, Chairman
Safety and Compensation Subcommittee
Committee on Education and Labor
House of Representatives
Washington, D. C.

Dear Mr. Wier:

I should like to take this opportunity to express the endorsement by the American Medical Association of H. R. 9822 and H. R. 11835, 85th Congress, bills to provide for holding a White House Conference on Aging and to assist states in conducting similar conferences on aging prior to the White House Conference.

The American Medical Association has had a deep and longstanding interest in the problems of our aged citizens, especially in regard to their health needs. Our Committee on Aging, established in 1955, is composed of some of the leading medical authorities in the country on the health problems of older persons. This Committee has recently conducted regional conferences on aging in Seattle, Dallas, Philadelphia, Birmingham, and Omaha. The American Medical Association has also scheduled a national conference on aging to be held in Chicago in September. Up to the present time, approximately thirty State Medical Societies have created Committees on Aging and by September it is expected that approximately forty such Committees will have been formed.

In addition to the activities of its Committee on Aging, the American Medical Association has recently joined with the American Dental Association, the American Hospital Association and the American Nursing Home Association in establishing a Joint Council to Improve the Health Care of the Aged. Although studies of the problems of the aged have been under way for the past several years by these various organizations, research in this field will now be intensified through joint efforts, and projects for meeting the problem will be activated as rapidly as possible.

The American Medical Association believes very strongly that there is a need for systematic interchange of ideas in this field. Through our experience with our regional conferences on aging and through our activities as a member of the Joint Council, we have learned that much is to be gained from state and national conferences on this subject, such as proposed in H. R. 9822 and H. R. 11835. The members of the medical profession will take part in these conferences, both on the state and national levels, to the fullest extent possible.

We are aware that the Committee is studying a number of bills which would establish a Bureau of Older Persons in the Department of Health, Education, and Welfare or a U. S. Commission on

Aging. The American Medical Association recommends that action on these bills be deferred until after the White House Conference on Aging. It may be anticipated that the Conference will include these bills in its deliberations.

I would request that this letter be made a part of the record of the hearings of your Committee and if your Committee desires any further information from our Association or the personal appearance of a representative, we would be most happy to comply.

Sincerely yours,
F. J. L. BLASINGAME, M.D.
General Manager

FEDERAL MEDICAL LEGISLATION

85th Congress

Social Security

An increasing number of bills relative to changes in Social Security are being dropped into the congressional hopper. Since many of the bills are similar or identical to previous bills, they will only be listed by number and author. References to similar bills which have been discussed previously will be given.

H. R. 10844 by Congressman Moore and H. R. 10869 by Congressman Neal (Republicans, W. Va.) are similar to S. 1811 by Senator Revercomb (R., W. Va.) and would provide a more liberal definition of "disability" for the purpose of receiving disability insurance benefits. Under this bill an individual who could not obtain employment because of his disability would be eligible for disability benefits.

H. R. 10845 and H. R. 10868 by Congressmen Moore and Neal, respectively, are similar to S. 1812 by Senator Revercomb (R., W. Va.) and apply to disability benefits and liberalization of the requirements, making an applicant eligible for benefits if he has "at least one quarter (3 months) of coverage."

H. R. 10974 by Congressman Dent, H. R. 10975 by Congressman Holland (Democrats, Pa.), and H. R. 10977 by Congressman Libonati (D., Ill.) are identical bills which would amend the Social Security Act to provide, among other things, increased benefits, and would increase the wage base and rate of tax. Retirement age would be reduced to age 60 for both men and women. The amendments would also eliminate age requirements for spouse benefits when the wage earner became eligible. Widows and widowers would also become entitled to benefits upon the death of the wage earner. Benefits would be increased, with the minimum benefit being $50 per month. Maximum family benefits would be increased from the present $200 to $250. The maximum income a recipient would be allowed to earn before suffering a reduction of benefits would be reduced from the present level of $1,200 to $600 annually. To pay for the increased benefits the base wage scale would be increased from the present rate of $4,200 to $5,000. In addition, the tax rate for both employee and employer would be increased by 0.5% for each, and by 0.75% for self-employed in 1959, 1960, and every 5 years thereafter until 1975. By 1975 self-employed with an income of over $5,000 would be paying $356.25 annually and the employed individual and his employer would each be paying $237.50 for social security coverage.

H. R. 11095 by Congressman Holtzman (D. N. Y.) is identical to H. R. 11396 by Congressman Dollinger (D., N. Y.), and both are similar to S. 173 by Senator Langer (R., N. D). These bills would eliminate the age 50 requirement for disability benefits, reduce the retirement age of men to 60 and for women to 55, and remove the limit of $1,200 that an individual could earn before benefits are reduced.

H. R. 11164 by Congressman Fino (R., N. Y.) is similar to H. R. 7834 by Congressman Shelley (D., Calif.) and would allow disability benefits for a survivor widow after age 50 if she becomes disabled.

S. 3419 by Senator Thye (R., Minn.) would eliminate the present requirement under the disability freeze and the disability benefits provisions of the Social Security Act, which requires that an individual must be covered for 5 out of the 10 years preceding the disability. An individual would still be required to be currently covered (coverage for 1½ years out of the 3 years preceding the onset of the disability) and also be fully insured (40 quarters of coverage or coverage for one-half the quarters since 1950, with a minimum of six quarters).

H. R. 11331 by Congressman Porter (D., Ore); H. R. 10664 by Congressman Ashley (D., Ohio); H. R. 10532 by Congressman Dellay (D., N. J.); and H. R. 9467 by Congressman Forand (D., R. I.) are all identical and have been previously discussed under the "Forand Bill." (The number of labor-dominated congressmen climbing on the band wagon continues to grow.)

H. R. 10730 introduced by Congressman Sheppard (D., Calif.) is similar to H. R. 5129 by Congressman King, H. R. 5278 by Congressman Roosevelt, H. R. 10820 by Congressman Doyle, and H. R. 10962 by Congressman Saund (Democrats, Calif.) and would provide for increased payments by the federal government to the states for carrying out the public assistance programs (aid to aged, dependent children, the blind, and the permanently and totally disabled). The government would contribute one-half of cost to the state for administration of the program and "one-half of the totals of sums expended . . . in the form of medical or any other type of remedial care. . . ." The bill would also remove the ceiling of the $60 maximum monthly payments now contained in the law. It would also require a state to participate in all four categorical programs in order to be eligible for payment under any one of the programs. It would enable

From the Washington Office of the American Medical Association.

an individual, eligible for benefits, but not meeting the necessary state residence requirements, to receive direct payment from the federal government in an amount equal to the government's contribution (including that for medical care) until such time as he can meet the state's residence requirement.

Anti-recession Measures

H. R. 10570 by Congressman McCarthy (D., Minn.) is similar to S. 3244 by Senator Kennedy (D., Mass.), and H. R. 11228 by Congressman Patterson (R., Conn.) and would change the unemployment compensation paid by states, by requiring that such states in order to qualify for federal grants, pay an amount equal to at least one-half of the average weekly wage, up to a maximum of two-thirds of the average weekly wage earned in the state, for a minimum period of 39 weeks. The bill would also provide grants to these states not providing such benefits for the 39-week period. This grant program would expire July 1, 1959. The increased cost of this bill would be provided by taxing every individual employing one or more persons the current excise tax of 3% of payroll up to the first $3,000 paid to any individual employee. This 3% tax would be paid entirely by the employer.

H. R. 10610 by Congressman Gregory (D., Ky.) is similar to H. R. 10706 by Congressman Roberts (D., Ala.) and would extend the time for hospital construction loans under the Housing Act of 1956 for construction of community facilities (including hospitals) in areas designated by the Office of Defense Mobilization.

H. R. 11272 by Congressman Rains (D., Ala.) is similar to S. 3497 by Senator Fulbright (D., Ark.) and identical to house bills H. R. 11273 to H. R. 11285, inclusive, and would establish an emergency community facilities and public work program in the Community Facilities Administration of the Housing and Home Finance Agency and would include, among other things, "public sanitary facilities, works for the treatment and purification of water . . . hospitals and other places for the care of the sick . . ." and would increase the loan fund used by this administration to purchase the securities of, or to make loans to municipalities and other subdivisions of states, to 2.5 billion dollars. The interest rate on these loans would be set at 2%.

S. 3450 by Senator Chavez (D., N. Mex.) would establish a Public Works Program to run for five years at a cost of approximately 14.5 billion dollars. Under these terms, the President would be authorized to provide, among other things, medical attendance and hospitalization for persons employed in projects located in remote and isolated areas.

H. R. 10703 by Congressman Rains (D., Ala.) would increase the money available for loans under the College Housing Program from the present 25 million dollars to 150 million dollars, for the construction of housing for student nurses and interns at nonprofit hospitals.

H. R. 11054 by Congressman Reuss (D., Wis.) would permit, under the Hill-Burton Hospital Construction Program, transfer of unused allotments of general hospital funds allotted to a state, for use in categorical programs (diagnostic treatment centers, chronic disease hospitals, rehabilitation facilities, and nursing homes), and would also allow the reverse transfer of funds from categorical programs to general hospital construction.

Health, Education, and Welfare

H. R. 10608 introduced by Congressman Fogarty (D., R. I.) on rehabilitation provides a new concept in that its goal is not limited to making a disabled individual employable but would broaden the Vocational Rehabilitation Act to provide "independent living rehabilitation services" by which the severely handicapped would be able to become more independent. These services are defined as "counseling psychological and related services . . . and . . . such term shall include physical restoration and related services, including corrective surgery, therapeutic treatment and hospitalization and other devices which will contribute to independent living. . . ." To provide these services 30 million dollars would be provided.

The bill would also authorize additional appropriations of $37,500,000 for three years. Under a formula, up to two federal dollars could be received for any one state dollar used for the construction of workshops and rehabilitation facilities.

H. R. 11057 introduced by Congressman Zablocki (D., Wis.) is similar to H. R. 383 by Congressman Rhodes (D., Pa.) and H. R. 11271 by Congressman Ullman (D., Ore.) would provide for the establishment of the Bureau of Older Persons within the Department of Health, Education, and Welfare and would authorize federal grants to assist in the development and operation of studies and projects to help older persons.

H. R. 11414 introduced by Rhodes (D., Pa.) supersedes an earlier bill (H. R. 6771) by the same author. Its purpose is to earmark one million dollars annually for grants-in-aid by the surgeon general of the Public Health Service for the support of public or nonprofit education institutions that provide training and services in the field of public health and administration of state and local public health programs.

Veterans Affairs

H. R. 10747 by Congressman Beckworth (D., Texas) would amend the Veterans' Benefits Act of 1957 by requiring the administrator of veterans affairs to ignore the employment status of a veteran who submits competent medical evidence to the effect that he is, in fact, totally and permanently disabled.

H. R. 10748 by Congressman Beckworth is similar to H. R. 6716 by Congressman Kee (D., W. Va.) and would prohibit the termination of a service-connected disability of 10% or more, for compensation, pension, and insurance purposes, which has been in effect for 10 or more years, except when based on fraud.

H. R. 10797 by Congressman Teague (D., Texas) would provide that any disability acquired, appearing, or recurring in active military service during a period of war, or the Korean conflict, after a veteran has continually served for 90 days shall be conclusively presumed to have occurred in or been aggravated by such service.

H. R. 10961 by Congressman Rogers (R,, Mass.) would provide ocular and dental outpatient treatment as though the condition were a service-connected disability for any veteran over 65 who has been in receipt of a pension for over one year.

H. R. 11181 by Congressman Christopher (D., Mo.) is similar to H. R. 9717 by Congressman Rogers (R., Mass.) and would deem tuberculosis a permanent and total disability during hospitalization as discussed in a previous report published in THE JOURNAL (**166**:1338 [March 15] 1958).

H. R. 11182 by Congressman Christopher (D., Mo.) would amend the Veterans' Benefits Act of 1957 by requiring that a veteran of World War I, World War II, or the Korean conflict be considered permanently and totally disabled at age 65 for pension purposes. Under present law, in order to qualify for a pension a veteran 65 years of age or older must have an impairment rated as 10% disabling.

H. R. 11364 by Congressman Long (D., La.) would provide certain adjustments in organization and salary structure of the Department of Medicine and Surgery in the Veterans Administration, mainly pay increases. The pay increases vary slightly from those provided for in H. R. 6719 also by Congressman Long (*J. A. M. A.* **164**:1581 [Aug. 3] 1957). Under the bill, H. R. 6719, optometrists would have an elevated rank in the Veterans Administration and be compensated at the same salary scale as physicians. Under the new bill, H. R. 11364, optometrists would be placed in the category of ancillary medical specialists such as "biologists, chemists, biostatisticians." As in H. R. 6719, lay managers of hospitals and domiciliaries would be paid the same rates as physicians in the chief grade. This bill would allow board certified medical specialists an increase of 17.5% of basic pay with the limitation that the salary not exceed $16,000.

Labor

H. R. 11286 introduced by Congressman Bosch (R. N. Y.) and S. 3443 by Senator Allott (R., Colo.) is similar to S. 2888 by Senator Douglas (D., Ill.) and would require the registration, reporting, and disclosure of employee welfare and pension benefit plans. An employee welfare benefit plan is defined as "any plan, fund or program . . . established by an employer or by an employee organization, or by both, for the purpose of providing for its participants or their beneficiaries, through the purchase of insurance or otherwise, benefits such as medical, surgical, or hospital care or benefits in the event of sickness, accident, disability, death or unemployment." Any plan that operated interstate or is operated by an organization "affecting commerce" or that is tax exempt, except tax exempt fraternal society plans, would be required to register with the Securities and Exchange Commission. Plans administered by the state or federal government or under workmen's compensation laws would be exempt from registration. Plans covering fewer than 100 employees would be exempt for two years after passage of the bill and for such longer period of time as the Securities and Exchange Commission may determine.

Those plans required to register would have to be registered within 90 days of passage of the bill or their establishment. The registration would be in a form prescribed by the Securities and Exchange Commission and would require names and addresses of individuals managing the plan and their relationship to the employer or employee organization, number of persons covered, type of benefits provided, source of financing, organization through which the benefits are provided, and whatever other information the Commission would require.

In addition, annual reports would be made listing the above information. Further, the annual report would have to show the amount of benefits paid, a detailed statement of assets, liabilities, receipts, disbursements, and other financial activities, the salaries and fees charged to the plan, to whom paid, in what amount, and for what purposes. If the benefits are provided by an insurance carrier, the carriers would be required to supply the plan managers with specified information.

The information provided in the registration or the annual report would be available to the public in the document rooms of the Commission. Copies of these reports would also be available to participants or beneficiaries at the offices of the plan and summaries of the reports would be provided to beneficiaries on request. The bill also provides for specific information to be contained in reports by pension plans.

An 11-man Advisory Council on Employee Welfare and Pension Plans to advise the Commission on carrying out its functions under the bill would be established.

The Securities and Exchange Commission would be given authority to make rules and regulations as may be necessary, use the information obtained to make statistical reports, and make studies for purposes of making legislative recommendations, such as the desirability of establishing standards for conducting plans and the instituting of civil suits against trustees for gross misconduct or abuses. The bill also provides specified penalties for specific violations.

Taxes

H. R. 10617 by Congressman Judd (R., Minn.) is similar to H. R. 10499 by Congressman Rains (D., Ala.), H. R. 10781 by Congressman Dellay (D., N. J.), and S. 3194 by Senator Sparkman (D., Ala.) on Tax Deferment of Annuities. S. 3194 was discussed in the last Federal Legislative Analysis.

H. R. 10904 by Congressman Curtis (R., Mo.) is similar to H. R. 490 by Congressman Thompson (D., N. J.) would provide a tax credit, under certain circumstances, against the income tax of 30% of the aggregate amount, up to $1,500, paid to institutions of higher learning as tuition or fees by an individual who is a full-time student.

H. R. 11011 by Congressman Fulton (R., Pa.) for tax exemptions for higher education is identical to H. R. 10026 by Congressman Sikes (D., Fla.) and S. 432 by Senator Fulbright (D., Ark.) and others discussed previously in the March 15, 1958, issue of THE JOURNAL, page 1338.

On the same subject with minor variations is the bill, by Congressman Nimtz (R., Ind.) H. R. 11018, similar to S. 433 by Senator Fulbright (D., Ark.) and H. R. 10543 by Congressman May (R., Conn.) and discussed in the last federal legislative analysis.

H. R. 11321 by Congressman Loser (D., Texas), H. R. 11187 by Congressman Cramer (R., Fla.), and S. 3415 by Senator Malone (R., Nev.) are identical to H. R. 9 by Congressman Jenkins (R., Ohio) and H. R. 10 by Congressman Keogh (D., N. Y.) commonly called the Jenkins-Keogh bill for Tax Deferment for Self-Employed which have previously been discussed extensively.

H. R. 11312 by Congressman Chamberlain (R., Mich.) would allow individuals a deduction up to $800, where income is less than $7,500, for tuition and fees paid on behalf of himself or a dependent while attending an institution above the 12th grade.

H. R. 11393 by Congressman Cramer (R., Fla.) would allow a credit of 30% of the aggregate amount, up to $400, against income tax paid by an individual in his own or another's behalf for tuition and fees in an educational institution above the 12th grade. The credit would not be allowed for individuals attending college on a scholarship, fellowship, grant, or under the GI Bill.

S. 3483 by Senator Thurmond (D., S. C.) is similar to the other bills introduced for tax credits for higher education. This bill would allow a taxpayer a credit of $100 against his income tax for himself, his spouse, or a dependent who is attending an institution of higher learning at least four months of a calendar year. Students under scholarship, fellowship, grant, or the GI Bill would be exempt.

Miscellaneous

H. R. 10694 by Congressman McFall (D., Calif.) would authorize withholding amounts for premiums on accident and health insurance contracts from salaries of any employee of federal government or District of Columbia at the request of individual employee. The premiums would be paid to an insurer chosen by the employee.

H. R. 10996 by Congressman Burdick (R., N. D.) is an anti-vivisection measure and would prohibit any person from engaging in the transportation in interstate commerce in the District of Columbia or territories, cats and dogs for vivisection, medical, or scientific experimentation. The bill would provide a fine of $1,000 and/or one year imprisonment for anyone convicted.

H. R. 11001 by Congressman Kilday (D., Texas), H. R. 11002 by Congressman Arends (R., Ill.), and H. R. 11003 by Congressman Vinson (D., Ga.) would amend the National Security Act by eliminating certain assistant secretaries of defense, including the Assistant Secretary for Health and Medical Matters (Dr. Frank Berry's office). Under these Defense Department Reorganization measures 14 assistant secretaries and 1,800 civilian employees would be eliminated. The A. M. A. was instrumental in having the office of the Assistant Secretary of Health and Medical Matters created in 1953 and is strongly opposed to its elimination.

S. 3481 by Senator Purtell (R., Conn.) would amend the Water Pollution Control Act with respect to limitations on grants for construction by increasing the amount of federal participation on certain projects. Under this proposal if the project were being carried on by two or more municipalities, the federal participation could equal $250,000 multiplied by the number of municipalities involved.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

POSTGRADUATE COURSES

The following course for physicians has not previously been listed by the Council. The following notice is presented for information only:

A five-day intensive lecture and clinical demonstration course for physicians, **Principles of Rehabilitation,** will be conducted June 16-20, 1958, at the Rehabilitation Center of the Hospital of the University of Pennsylvania, in cooperation with the Office of Vocational Rehabilitation, United States Department of Health, Education, and Welfare. Registration will be limited. A limited number of $100 trainee stipends, provided by the United States Office, may be granted to eligible physicians. Inquiries or applications may be addressed to the Rehabilitation Center, Hospital of the University of Pennsylvania, Philadelphia 4.

MEDICAL NEWS

CALIFORNIA

Dr. Cullen Comes to San Francisco.—Dr. Stuart C. Cullen, professor of surgery and anesthesiology, State University of Iowa College of Medicine, Iowa City, has been appointed professor of anesthesiology and chairman of that department in the University of California School of Medicine, San Francisco. Dr. Cullen had been chairman of the division of anesthesiology at the University of Iowa since 1938. He is president-elect of the Society of University Anesthetists.

Personal.—Dr. Sidney S. Sobin, Los Angeles, research professor of medicine, College of Medical Evangelists School of Medicine, was recently appointed a consultant in cardiology by the State Board of Public Health, to serve the California State Department of Public Health in an advisory capacity during 1958.——Dr. Edwin Barnett, who recently became director of the Palo Alto–Stanford Hospital Center, has been named professor of hospital administration at Stanford Medical School. The hospital center will be part of the now-building Stanford Medical Center on the campus. Dr. Barnett currently runs the 200-bed Palo Alto Hospital.——Dr. Edward J. Zaik has been appointed associate medical director, the Pacific Telephone and Telegraph Company, Southern California. He assumed his new duties April 1.

County Mental Health Program.—Dr. Mervyn Shoor has accepted the position of program chief, Community Mental Health Services, Santa Clara County, San Jose effective full time July 1, at which time he will resign as chief psychiatrist, Fresno State Mental Hygiene Clinic. The new position was created by Santa Clara County's adoption of the Community Mental Health Services as part of its implementation of the recent Short-Doyle legislation, designed to provide local communities with Mental Health Services on a fifty fifty, (state-local) matching-fund basis. The administrator of the new program is Dr. W. Elwyn Turner, public health officer of Santa Clara County. The new program initially will offer clinic psychiatric outpatient services, extramural consultation to other agencies (medical, social, law enforcement, etc.), as well as a limited amount of child guidance services.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

FLORIDA

Medical Research Unit at Coral Gables.—Construction of the Medical Research Unit of the University of Miami School of Medicine, Coral Gables, started May 5. The building will cost $2,150,000, of which $990,000 was provided by a bond issue for construction at Jackson Memorial Hospital approved by voters in 1953 and released by the county recently after the university received a construction grant of $941,720 from the Surgeon General's Office of the U. S. Department of Health, Education and Welfare. The remaining $218,280 needed will be provided from funds available within the university. The eight-story unit will house laboratories for all phases of medical research and the first unit of the permanent medical library. Located immediately south of the outpatient clinic at Jackson, it will be on the corner of N. W. 10th Avenue and 16th Street. Completion date is estimated at 15 months. Funds needed for construction of the instructional wing of the building to adjoin its west side (estimated at $2,850,000) are still being sought.

ILLINOIS

Birth Rate at All-Time High.—The Illinois Department of Health has announced that more babies were born alive in Illinois in 1957 than in any previous year. Provisional statistics indicate a total of about 240,000 live births, an increase of more than 10,000 over the 1956 figure. Last year's provisional birth rate, at 24.6 per 1,000 population, is also the highest ever recorded. The number of deaths in Illinois in 1957 (about 102,000) was less than half the births, giving the state a natural increase in population of about 138,000. The state's provisional death rate for 1957 was 10.5 per 1,000 population, slightly higher than the 1956 figure of 10.2. Maternal mortality last year continued at the very low level of 3 deaths per 10,000 live births, the same as was recorded in 1956. This is less than one-third the rate a decade ago when 10 mothers died for every 10,000 babies born alive. As to infant mortality, provisional figures indicate a slight increase in the 1957 rate, 24.6 deaths per 1,000 live births, compared with a rate of 24.2 in 1956. In 1947 infant deaths in the state occurred at a rate of 29 per 1,000 live births.

Chicago

Annual Irons Lecture.—Nu Sigma Nu Fraternity, Kappa Chapter, will present the annual Ernest E. Irons Lecture June 10 5 p. m., in Room P-117,

Billings Hospital, when Karl P. Link, Ph.D., professor of bacteriology, University of Wisconsin, Madison, will speak on "Anticoagulants—Where Are We Now?"

Visiting Professor at La Rabida.—Howard J. Rogers, Ph.D., of the Medical Research Council at the National Institute for Medical Research, Mill Hill, London, England, is visiting professor at the La Rabida–University of Chicago Institute for the quarter ending June 14. Dr. Rogers is deputy chairman of the editorial board of the *Biochemical Journal.*

Contributions for Cancer Research.—The Nathan Goldblatt Research Fund has presented to the University of Chicago $100,000, the first payment on a new pledge of $250,000 which will contribute to expansion of the university's cancer research facilities. In addition, the Nathan Goldblatt Society for Cancer Research has pledged $100,000 toward the cost of the new unit of the University Clinics. The new building, two stories and a basement, will connect the Chicago Lying-in Hospital with Bobs Roberts Memorial Hospital for Children. By permitting relocation of outpatient service, it will provide space for expansion of research in cancer and other diseases in Billings Hospital of the clinics. Since 1948, following a gift of one million dollars from the Goldblatt Brothers Foundation in 1947 for the Nathan Goldblatt Memorial Hospital, Goldblatt Brothers Employees Organization grants toward cancer research at the university have totaled $419,000, and the Nathan Goldblatt Society support is about $440,000.

INDIANA

Summer Camp for Diabetic Children.—The Indianapolis Diabetes Association will sponsor the James Whitcomb Riley camp for diabetic children for the fourth consecutive year. The camp session will open Aug. 3 and conclude Aug. 22. The facilities of the Riley Memorial Association and Indiana University will be used. The camp is in the Brandford Woods Outdoor Education area six miles north of Martinsville near State Highway 67. Diabetic children from 8 through 16 years of age are eligible. The program will be conducted on a nonsectarian basis without restrictions as to race or creed. Campers will be under constant medical and nursing care; qualified dietitians will supervise meals; and a laboratory will be operated for all necessary tests incident to the control of diabetes. Applications will be received only for the full session. The fee for the three weeks is $150, which includes all diabetic supplies and necessary laboratory procedures. Funds are available for financial assistance to children whose families are unable to pay the full amount. Information may be obtained from the Indianapolis Diabetes Association, Inc., 821 Hume Mansur Building, Indianapolis 4, Ind.

MASSACHUSETTS

Award Cancer Grant to Dr. Wotiz.—Herbert H. Wotiz, Ph.D., associate director, hormone research laboratory, Boston University School of Medicine, has been awarded a $115,000 grant by the U. S. Public Health Service for a four-year study on the functions of hormones in relation to cancer. The research is part of a continued study by Dr. Wotiz and the school laboratory. Dr. Wotiz and three associates were awarded first prize in the section of experimental medicine and therapeutics at the A. M. A. meeting in New York last summer for an exhibit of "Estrogen Biosynthesis by Post-Menopausal Human Ovaries."

Personal.—Dr. Robert S. Schwab has been elected chairman of the Medical Advisory Board of the Myasthenia Gravis Foundation. Dr. Schwab, neurologist at the Massachusetts General Hospital since 1937, has served on the executive committee of the foundation's medical board since its inception in 1952.——Dr. Helmuth Ulrich, of Newton, has received the "Man of the Year" award of the Boston University Medical School Alumni Association. Dr. Ulrich, who graduated in 1911, is the fifth alumnus to receive the citation.——Dr. Merrill C. Sosman, emeritus professor of roentgenology, Harvard Medical School and emeritus roentgenologist-in-chief of the Peter Bent Brigham Hospital, Boston, gave the fourth annual W. J. and C. H. Mayo Memorial Lecture on "The Accuracy of X-Ray Diagnosis" at Carpenter Hall, Dartmouth College, Hanover, N. H., March 29.

NEW JERSEY

Establish Kump Memorial Grant.—The board of trustees of the Medical Society of New Jersey has authorized the establishment of the Albert Barker Kump Memorial Grant in the Medical Student Loan Fund of the society. The goal is $5,000. Dr. Kump, who was president of the society, died April 18. Contributions (payable to the society) and requests for information should be sent to The Albert Barker Kump Memorial Grant, the Student Loan Fund of the Medical Society of New Jersey, P. O. Box 904, Trenton 5, N. J.

Personal.—Governor Robert B. Meyner has announced the appointment as of March 14 of Dr. Luke A. Mulligan to the State Board of Medical Examiners for a term of three years.——Dr. Charles Hendee Smith has become a member of the Princeton Medical Group. He will continue to see patients in consultation in the New Brunswick Pediatric Group in which he has practiced for the last 16

years. Dr. Smith is 81.——The Secretary of the British Medical Association invited Dr. Edward M. Miller, of Englewood, to deliver the Annual British Medical Association Lecture to the North Middlesex Division of the B. M. A. on March 31. His subject was "Surgical Management of Carcinoma of the Colon."

New Medical Center in Livingston.—Ground-breaking ceremonies for a 10-million-dollar "hospital of tomorrow" were held May 3 in Livingston. Trustees of Saint Barnabas Medical Center, Newark, said that patients in the new center will be grouped according to the intensity of illness, made possible by three separate patient areas: (1) an admission area where patients will be admitted to a private or semiprivate room on the ground floor to remain until tests are completed and diagnosis is determined; (2) An intensive care area where all surgical patients will go for special care immediately after leaving the recovery room; (3) A convalescent area on an upper floor for patients no longer needing intensive care. On the ground floor will be the admission area, intensive care area, and operating, cystoscopic, and fracture rooms, recovery room, clinical and x-ray laboratories, outpatient and rehabilitation departments. According to the trustees, this will enable one-third more patients to be treated without increasing the number of personnel. The new center, located on 60 acres overlooking the Kittatiny mountain range, will be a nondenominational, nonprofit general hospital with 400 beds and 75 bassinets. The project will be completed in 1959-1960.

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NEW YORK

Inaugurate President at Upstate Medical Center.—Carlyle F. Jacobsen, Ph.D., will be inaugurated as first president of the State University of New York Upstate Medical Center in Syracuse at commencement exercises June 8, 2:30 p. m., in Nottingham Auditorium. Welcoming Dr. Jacobsen to office on behalf of the faculty will be Wilfred W. Westerfeld, Ph. D., chairman, department of biochemistry, and formerly acting dean of the Center. Dr. Jacobsen assumed the post of president of the center and dean of its College of Medicine on Dec. 1, 1957. He was previously executive dean for medical education of the State University of New York.

Personal.—The University of Buffalo School of Medicine and Buffalo General Hospital honored Dr. Thomas F. Frawley, head, sub-department of endocrinology and metabolic diseases, Albany Medical College, when they chose him as their first visiting professor for a week, April 14-20.——Dr. Victor N. Tompkins has been appointed assistant commissioner of health for the State Health Department's Division of Laboratories and Research, effective April 1, succeeding Dr. Gilbert J. Dalldorf, who left to become associate medical director of the National Foundation for Infantile Paralysis in January.——Bernard Saper, Ph.D., has been appointed director of psychological services in the New York State Department of Mental Hygiene, succeeding Elaine F. Kinder, Ph.D. He will assume his duties July 1.——Franklyn N. Arnhoff, Ph.D., clinical assistant professor of psychiatry, Syracuse University College of Medicine, has been granted a faculty fellowship in social gerontology by the Inter-University Council on Social Gerontology of the University of Michigan, Ann Arbor, for advanced study in gerontology for the month of August at the University of Connecticut, New Haven.

New York City

Dr. Dubos Wins Ricketts Award.—Rene J. Dubos, Ph.D., bacteriologist, Rockefeller Institute for Medical Research, received the Howard Taylor Ricketts award for 1958 recently at the University of Chicago when he lectured on "Nutrition, Emotion and Infection." The prize, consisted of a medal and a cash stipend of $200. Born and educated in France, Dr. Dubos came to the United States in 1924, and he has been associated continuously with the Rockefeller Institute of Medical Research since 1927 except for two years when he was George Fabyan professor of comparative pathology and tropical medicine at Harvard Medical School, Boston. The Howard Taylor Ricketts award was established by Mrs. Howard T. Ricketts in memory her husband who died May 3, 1910, in Mexico City while doing research on typhus fever. He was a prominent faculty member of Rush Medical College.

NORTH CAROLINA

Courses in Air Pollution.—The University of North Carolina's Department of Sanitary Engineering in the School of Public Health, Chapel Hill, has announced courses in air hygiene and air pollution control made possible under a grant from the U. S. Public Health Service. The first of these courses has been initiated, with expansion to three during the 1958-1959 school year. The plan provides a concentration in air pollution control based on the principles of air hygiene, which may concurrently fill the prerequisites for courses in industrial hygiene. Inquiries should be addressed to Prof. Daniel A. Okun, Box 899, Chapel Hill, N. C.

Open Another Poison Control Center.—The second Poison Control Center in the State opened at Onslow Memorial Hospital in Jacksonville May 1. Dr. Samuel C. Cox is director of the center and Dr. Eleanor H. Williams, Onslow County Health Director, is assistant director. The telephone numbers are 7241 & 7242. The center will be able to provide information as to ingredients, toxicity, symptoms, and preferred treatment of many of the potentially poisoning trade-name products. The Onslow Poison

Control Center is making its services available specifically to all physicians in the Third District of the State Medical Society and to any others who may wish to use it.

Students Win Pathology Awards.—Two fourth-year medical students of the University of North Carolina School of Medicine, Chapel Hill, have won awards in nation-wide competition for papers presented on research they did in the field of inheritance of human diseases. They are W. R. Bullock Jr., of Bethel, and Vernon McFalls, of Greensboro. Both received Sheard-Sanford prizes which are presented annually by the American Society of Clinical Pathologists in the form of cash grants. Their work was done under the supervision of Dr. John B. Graham, associate professor of pathology at the Medical School. Bullock's paper was on "Carrier State of Plasma Thromboplastin Component Deficiency," while McFalls' paper dealt with "Genetic Study of Vitamin D, Resistant Rickets and Hypophosphatemia."

PENNSYLVANIA

Philadelphia

Students Win Research Awards.—Five University of Pennsylvania medical students received special prizes and awards at the Medical School's 50th annual Undergraduate Medical Association Day, April 24. The awards are annual honors to medical students doing "the best medical research" in various fields of interest:

The annual Borden Undergraduate Research Award in Medicine ($500) awarded to Stanley M. Boulas, of Providence, R. I., is presented to that member of the fourth-year class "whose research has been determined to be the most meritorious performed by all similarly eligible persons."

The Mary Ellis Bell Prize, presented to Robert Byck, a junior medical student from Newark, N. J., was presented "for outstanding medical research."

The Rose Meadow Levinson Memorial Prize was awarded to William H. Hardesty, senior medical student from Northfield, Minn., for his presentation of the "best paper dealing with cancer."

Theodore R. Bledsoe, junior medical student from Silver Spring, Md., won the John G. Clark prize "for the best paper dealing with obstetrics and gynecology."

The O. H. Perry Pepper Prize, given to Gordon B. Avery, of Washington, D. C., is presented to the medical senior "who has performed investigative work of exceptional merit during his four years, and who has also demonstrated noteworthy competence as a clinician."

WISCONSIN

Institute on Alcohol Studies.—The third annual meeting on alcohol problems, sponsored jointly by the University of Wisconsin Extension Division, Western Michigan University, the Wisconsin Council on Alcoholism, and the Michigan State Board of Alcoholism, will be held June 23-27. Keynote speaker, Selden D. Bacon, Ph.D., professor of sociology, Yale University, New Haven, Conn., will open the institute with a discussion on "Problems of Alcohol Orientation." Discussion topics include: physiological, social, economic, educational, and legal aspects of the alcohol problem. A special feature will be a teenage panel discussing problems of teenage drinking. Information may be obtained from Prof. John L. Miller, Ph.D., director, 1958 Midwest Institute on Alcohol Studies, 206 Extension Building, Madison 6, Wis.

GENERAL

Fellowships in Psychiatry.—The American Psychiatric Association has announced the award of 10 Smith Kline & French Foundation fellowships in psychiatry totaling $13,150, which are the final awards of the three-year $90,000 grant established in 1955 to provide a broad range of training opportunities in psychiatry. The foundation recently awarded a $100,000 grant to the American Psychiatric Association to continue the fellowships through 1960. A total of 14 recipients, including 10 medical students, will benefit in the latest group of grants. The fellowships are administered by a committee named by the association, with Dr. Kenneth E. Appel, Philadelphia, as chairman.

International Prize for Medical Ethics.—The "John XXI" International Prize for Medical Ethics, instituted at the Paris Congress in 1951 by the Association of Portuguese Catholic Doctors, has been announced by the International Secretariate of Catholic Doctors. The competition theme will be "Responsibility of the Doctor Before the Actual World" and the following rules apply:

(1) The prize will consist of a bronze medal and a sum of 5000 Belgian franks or the equivalent.

(2) The prize will be awarded at the Eighth International Congress of Medical Doctors to the best work on medical ethics concerning the theme of the competition. The work must be supplied with a typed translation in English or French in seven copies. The work must include 20 to 30 pages with about 25 lines on a page.

(3) The competitors should send their work to the International Secretary, 5, rue Guimard, Brussel, before July 1, together with an application for admission.

Medical Education Tour of South America.—Dr. Carl F. Schmidt, chairman, department of pharmacology, University of Pennsylvania, is one of three medical scientists appointed by the International Union of Physiological Sciences to visit South America to discuss problems of medical education and research. Dr. Schmidt left May 14 to join Drs. C. Heymans, professor of pharmacology, University of Ghent, Belgium, and Ragnor A. Granit, professor of physiology, Karolinska Institute, Stockholm, Sweden, for a six-week tour of South American medical education and research facilities. The three-man team of the International Union, an affiliate of the World Health Organization, will

visit medical schools and facilities in Venezuela, Brazil, Uruguay, Argentina, Chile, Peru, Colombia, Panama, and Mexico. During the tour, Dr. Schmidt will appear at the various medical schools as a guest lecturer. A member of the National Academy of Sciences and a past-president of the American Society for Pharmacology Dr. Schmidt is also editor-in-chief of *Circulation Research*.

Meeting of Medical Women in San Francisco.—The annual meeting of the American Medical Women's Association, will be held June 19-22, with headquarters at the Sir Francis Drake Hotel, San Francisco. The Woolley Memorial Lecture will be presented June 20, 7 p. m., by Dr. Jessie M. Bierman, of the University of California School of Health, San Francisco. Following presentation of the Elizabeth Blackwell award by Dr. Alma D. Morani, Dr. Katharine W. Wright, president of the Association, will present an inauguration address, "Group Participation—Keynote of the Future." A luncheon panel on "The Physician in the Role of Advisor," moderated by Dr. Rosa Lee Nemir, will include the following subtopics and participants:

In the Home, Dr. Judity E. Ahlem, Livermore, Calif.
In High School, Dr. Mary A. M. Henry, San Antonio, Texas.
In College, Dr. Mary S. K. Helz, State College, Pa.
In the Community, Dr. Jessie Laird Brodie, Portland, Ore.
In the Physician's Office, Dr. Camilla M. Anderson, Salt Lake City, Utah.

A program of entertainment is arranged. For information write the American Medical Women's Association, Inc., 1790 Broadway, Room 315, New York 19.

Announce Six Ophthalmology Fellowships.—Six fellowships for residents in ophthalmology, to begin July 1, have been announced by the Guild of Prescription Opticians of America, Inc. Applications for these fellowships must be received by June 13. Each fellowship is for a total of $1,800, payable in monthly stipends over the period of a three-year residency. The grants are limited to residencies at approved institutions where full three-year residencies are offered. Each grant is made for the entire three years, to begin the first year. Application forms are available by writing Fellowships, Guild of Prescription Opticians of America, Inc., 110 E. 23rd St., New York 10. The new fellowships represent one for each of six areas into which the U. S. and Canada have been divided on the basis of a nearly equal number of eligible residencies in each area. The selection of the resident fellow is made by a committee of ophthalmologists in each area. The guild provides all fellowship funds as well as the program's cost of administration. Together with the 6 guild fellowships awarded in 1956 and the 5 last year, this year's new fellowships will bring the total to 17.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	May 10, 1958 Paralytic Type	May 10, 1958 Total Cases	May 11, 1957 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	1
Massachusetts	..	..	1
Rhode Island	..	..	..
Connecticut	..	..	1
Middle Atlantic States			
New York	..	..	1
New Jersey	..	1	..
Pennsylvania	..	..	2
East North Central States			
Ohio	..	..	1
Indiana	..	..	..
Illinois	..	..	..
Michigan	..	..	..
Wisconsin	..	..	1
West North Central States			
Minnesota	..	..	1
Iowa	..	..	..
Missouri	..	..	2
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	..	1
Kansas	..	..	1
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	1
West Virginia	..	..	..
North Carolina	..	..	..
South Carolina	..	..	..
Georgia	..	..	..
Florida	..	..	5
East South Central States			
Kentucky	..	..	1
Tennessee	..	1	..
Alabama	..	..	..
Mississippi	..	3	2
West South Central States			
Arkansas	..	..	1
Louisiana	..	..	8
Oklahoma	..	..	..
Texas	4	5	15
Mountain States			
Montana	..	..	..
Idaho	..	..	1
Wyoming	..	..	3
Colorado	..	1	..
New Mexico	..	..	2
Arizona	1	3	1
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	..
California	2	5	18
Territories and Possessions			
Alaska	..	..	..
Hawaii	..	..	..
Puerto Rico	3	3	..
Total	10	22	71

Meeting on Goiter in San Francisco.—The 1958 annual meeting of the American Goiter Association will be held in the St. Francis Hotel, San Francisco, June 16-19. On June 16 operative clinics, and a panel discussion, "Carcinoma of the Thyroid Gland," will be held at Moffitt Hospital. Forty-four papers are scheduled for the five sessions, including the following by foreign authors:

Functional Relation Between the Liver, the Thyroxine-Binding Protein, and the Thyroid, Dr. Alfred Vannotti, Lausanne, Switzerland.
Studies on the Effect of TSH on Human Thyroid Function, Drs. Jerzy Einhorn and Lars Gunnar Larsson, Stockholm, Sweden.
Hypothalamic–Adrenal–Thyroid Relationships, Dr. Geoffrey W. Harris, London, England.

Dr. Elmer C. Bartels, Boston, will present the presidential address the afternoon of June 18. A ladies' program is arranged. For information write the American Goiter Association, Dr. John C. McClintock, Secretary, 149½ Washington Ave., Albany, N. Y.

Endocrine Society Meeting in San Francisco.—The 40th annual meeting of the Endocrine Society will be held in the St. Francis Hotel, San Francisco, June 19-21. Over 80 papers are scheduled for presentation at seven sessions under the following headings: endocrine and metabolic interrelationships, thyroid and parathyroids, adrenal and gonads, pituitary and hypothalamus, gonads and reproduction, diabetes and metabolism, and adrenal. The eighth session will be devoted to clinical panels with the following chairmen:

Endocrine Treatment of Neoplastic Disease, Dr. Olof H. Pearson, New York City.
Hyperparathyroidism and Bone Disease, Dr. Gilbert S. Gordon, San Francisco.
Chemical Treatment of Diabetes, Dr. Peter H. Forsham, San Francisco.
Intersexuality, Dr. Warren J. Nelson, Safford, Ariz.

Leo T. Samuels, Ph.D., will present the presidential address at the annual dinner, June 20, 7:30 p. m. For information write Dr. Henry H. Turner, 1200 N. Walker St., Oklahoma City 3, Okla., secretary of the society.

Fellowship in Heart Research.—The American Heart Association has announced the award of $1,433,147 to 183 scientists for research on heart and blood vessel diseases. Continued emphasis will be given in these studies to basic research in factors underlying disorders of the heart and circulation. Support will also be given for investigators working on a wide range of problems affecting the welfare and treatment of heart patients. The awards go into effect on July 1. Dr. Robert W. Wilkins, president of the association, pointed out that all these awards were made possible by voluntary public contributions to the annual Heart Fund appeal and they represent the first part of the 1958-1959 national research support program. A second group of national awards, in the grant-in-aid category, will be announced within the next few months. The 183 scientists named will pursue their studies in 29 states, the District of Columbia, England, and Denmark. Eighty-four of the awards are to "established investigators" (this category provides five years of uninterrupted support to mature scientists conducting independent research). Sixty-two of the awards are to research fellows; thirty-four to advanced research fellows. Given usually for two years, both of these fellowships enable young scientists to obtain training in research methods under experienced guidance. In addition, $59,000 was appropriated in departmental grants to help meet overhead costs incurred on behalf of established investigators.

Awards for Student Exhibits.—The first Student American Medical Association–Lakeside Laboratories awards, presented for "outstanding medical exhibits," were given to three exhibits at the Student A. M. A. meeting in Chicago recently. Top awards of $500 each plus the privilege of exhibiting their work at the American Medical Association convention in San Francisco, including a free trip to and week in that city, went to (1) Quinton Callies, junior of the University of Wisconsin School of Medicine, Madison, for his exhibit on work with Drs. Helen A. Dickie and John I. Rankin on "Farmer's Lung"; (2) Dr. Edward R. Duffie, intern at the Raymond Blank Memorial Hospital in Des Moines, Iowa, for an exhibit of work in endocardial fibroelastosis. The second and third student awards of $350 and $250, respectively, went to (1) Michael P. Kaye and Robert A. McDonald, of the Stritch School of Medicine of Loyola University, Chicago, for "Cardiac Augmentation," and (2) Olga Jonasson and Robert P. Hodam, of the University of Illinois Medical School, Chicago, for "The Viability of Cancer Cells in the Circulating Blood of Animals."

Conference on Cell Organization.—A conference on "The Chemical Organization of Cells, Normal and Abnormal" will be held in Madison, Wis., Aug. 21-23, supported by the National Institutes of Health as part of the program for increase in pathology research potential. Speakers include George O. Gey, Paul A. Weiss, Ph.D., Van R. Potter, Ph.D., Charles D. Kochakian, Ph.D., Albert J. Dalton, Ph.D., Dr. Sheldon C. Sommers, Choh H. Li, Ph.D., G. H. Bourne, Dr. Frederik B. Bang, David E. Green, Ph.D., Alfred G. Marshak, Ph.D., Dr. Henry Quastler. Interested persons should write Dr. Joseph J. Lalich, professor of pathology, University of Wisconsin, 426 N. Charter St., Madison, Wis. The National Institutes of Health has made funds available for a limited number of stipends to assist workers in basic science fields in attending the Madison conference. This money will be available after the first of July and will include the fees for the conference and up to a maximum of $200 for transportation. These funds are intended to support the travel and attendance of younger workers (a) in junior academic or research positions and (b) not already in recipt of research grants carrying stipends. Application should be made in writing to Dr. Joseph F. A. McManus, Chairman, Department of Pathology, University of Alabama Medical Center, Birmingham, Ala. A letter from the chair-

man of the department should accompany each plication. Requests for accommodation should made to Dr. Lalich at the same time.

Meeting on Electroencephalography in Atlantic City.—The 12th annual meeting of the American Electroencephalographic Society will be held June 12-15 at the Hotel Traymore, Atlantic City, N. J. Dr. Robert S. Dow will give the presidential address the morning of June 14 and will serve as chairman for a symposium on "Electrophysiology of the Cerebellum," which will include the following topics and participants:

Introduction and Historical Survey, Dr. Dow.
Cerebellar Responses to the Stimulation of Afferent Connections, Dr. Ferdinando A. Morin, Detroit.
Electrical Activity of the Cerebellar Cortex and Nuclei and How It May Be Modified, John M. Brookhart, Ph.D., Portland, Ore.
Efferent Discharges Resulting from Electrical Stimulation of the Cerebellar Cortex and Nuclei, Ray S. Snider, Ph.D., Chicago.
Significance of Electrophysiological Studies in Relation to the Localization of Function in the Cerebellum, Dr. William W. Chambers and James M. Sprague, Ph.D., Philadelphia.
Relation of the Cerebellum to Sensory Mechanisms, Dr. Dow.

Twenty-five papers are scheduled and a symposium on EEG of the "Premature, Newborn and Young Infant" is planned for June 15. Speaker at the annual banquet (June 14, 7 p. m.) will be Donald B. Lindsley, Ph.D., who will discuss "Lindsley's Folly: Reminiscences About the Early Days of EEG During the Depression Era (1930-1940)." For information write Dr. Jerome K. Merlis, Secretary, American Electroencephalographic Society, EEG Laboratory, University Hospital, Baltimore 1, Md.

FOREIGN

International Meeting of Gynecologists and Obstetricians.—The International Professional Association of Gynecologists and Obstetricians will meet in Brussels, Belgium, under the presidency of Dr. Francisco Luque Beltrán, of Madrid, July 18-19. Two main subjects to be discussed are: "Criteria and Processes of Specialization in Gynecology and Obstetrics" and "Economic Classification of Fees for Obstetric and Gynecologic Functions According to the Hierarchy of Values." Registration fee is 500 Belgian francs to be deposited to the account of l'Association Professionnelle des Obstetriciens et Gynecologues Belges: Dr. Stocq, 23 Dréve du Caporal Uucle, Banque de la Société Générale de Belgique, Brussels, Belgium. Information can be requested from the General Secretary of the Congress, Dr. Geeraert, 211, Avenue Louise, Brussels, Belgium.

DEATHS IN OTHER COUNTRIES

Tobias Levitt.—Formerly surgical first assistant at the thyroid clinic, New End Hospital, Hampstead, England, Tobias Levitt, F. R. C. S., died in Charing Cross Hospital Feb. 22. He was elected to give a Hunterian Lecture at the Royal College of Surgeons (1952), was author of "The Thyroid: A Physiological, Pathological, Clinical, and Surgical Study," and was attached to the Royal Marsden Hospital in a research capacity (since 1956). He was awarded a travelling fellowship by the Kellogg Foundation and by the International College of Surgeons, spending a year in the U. S. lecturing on diseases of the thyroid.

CORRECTIONS

Occupational Cancer.—In the report to the Council on Industrial Health in the April 26, 1958, issue of The Journal, Page 2177, column 1, second new paragraph, the equation starting on line 3 should read as follows: "Incidence (cases per 100,000 per year) = [total number of cases for n years ÷ (population at risk × n)] × 100,000." The equation starting on the fifth line from the end of the same paragraph should read: "Incidence = [10 ÷ (100 × 10)] × 100,000 = 1,000 per 100,000 per year."

Aero Medical Association.—In the Washington News in The Journal, Feb. 22, 1958 issue, front advertising page 27, and April 5, 1958 issue, front advertising page 27, it was stated that the Aero Medical Association was "now nine years old" and was "formed ten years ago," respectively. These statements were erroneous. The Aero Medical Association was founded in 1929. The 30th anniversary will be observed at the association's annual meeting in Los Angeles, April 27-29, 1959.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates, Inc.: The American medical qualification examination to be given henceforth twice a year for foreign medical graduates. Medical Schools in the United States and Foreign Countries, Sept. 23. Final date for filing application is June 23. Executive Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Illinois.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: *Written. Parts I and II.* All medical centers in the United States and Canada, June 17-18. Sec., Dr. John P. Hubbard, 133 S. 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alabama: *Examination.* Montgomery, June 17-19. Sec., Dr. D. G. Gill, State Office Building, Montgomery 4.
Arizona:* *Examination.* Phoenix, July 16-18. *Reciprocity.* Phoenix, July 19. Sec., Dr. Thomas N. Bate, 826 Security Bldg., Phoenix.
California: *Written Examination.* San Francisco, June 16-19; Los Angeles, August 18-21; Sacramento, Oct. 20-23. *Oral Examination.* San Francisco, June 14; Los Angeles,

August 16; San Francisco, November 15. *Oral and Clinical Examination for Foreign Medical School Graduates.* San Francisco, June 15; Los Angeles, August 17; San Francisco, November 16. Sec., Dr. Louis E. Jones, 1020 N Street, Sacramento.

COLORADO:* *Examination and Reciprocity.* Denver, June 10-11. Exec. Sec., Mrs. Beulah H. Hudgens, 715 Republic Bldg., Denver 2.

CONNECTICUT:* *Examination.* Hartford, July 8-10. Sec., Dr. Creighton Barker, 160 St. Ronan St., New Haven.

DELAWARE: *Examination and Reciprocity.* Dover, July 8-10. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

FLORIDA:* *Examination.* Miami, June 29-July 1. Sec., Dr. Homer L. Pearson, 901 N. W. 17th St., Miami.

GEORGIA: *Examination.* Atlanta and Augusta, June 11-12. *Reciprocity.* Atlanta, June 13. Sec., Mr. C. L. Clifton, 224 State Capitol Bldg., Atlanta.

IDAHO: *Examination.* Boise, July 14-16. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Written Examination.* Chicago, July 7-11. *Oral Reciprocity Examination.* Chicago, July 11. Supt. of Regis., Mr. Frederic Selcke, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 18-20. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

IOWA:* *Examination.* Iowa City, June 16-18. Exec. Sec., Mr. Ronald V. Saf, State Office Bldg., Des Moines 19.

KANSAS:* *Examination.* Kansas City, June 13-14. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

KENTUCKY: *Written Examination.* Louisville, June 9-11. Sec., Dr. Russell E. Teague, State Board of Health, Louisville 2.

MAINE: *Examination.* Augusta, July 8-10. *Reciprocity.* Augusta, July 8. Sec., Dr. Adam P. Leighton, 142 High St., Portland.

MARYLAND: *Examination.* Baltimore, June 17-20. Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination.* Boston, July 15-18. Sec., Dr. Robert C. Cochrane, Room 37 State House, Boston.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June 9-11. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., West Michigan Ave., Lansing 8.

MINNESOTA:* *Examination.* Minneapolis, June 17-19. *Reciprocity.* Minneapolis, June 19. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Examination.* Jackson, June 23-24. *Reciprocity.* Jackson, June 25. Asst. Sec., Dr. R. N. Whitfield, Old Capitol Bldg., Jackson 113.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 7. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 16-18. Sec., Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEW HAMPSHIRE: *Examination.* Concord, Sept. 10-13. *Reciprocity.* Concord, Sept. 10. Sec., Dr. Mary M. Atchison, Room 101, 61 South Spring St., Concord.

NEW JERSEY: *Examination.* Trenton, June 17-20. Sec., Dr. Patrick H. Corrigan, 28 W. State St., Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York City and Syracuse, June 24-26. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Examination.* Raleigh, June 16-19. *Reciprocity.* Raleigh, June 17 and Blowing Rock, July 25. Asst. Sec., Mrs. Louise J. McNeill, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 9-11. *Reciprocity.* Grand Forks, July 12. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* June 19-21, Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

OREGON:* *Examination.* Portland, July 16-17. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland 4.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 8-10. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, June 26-27. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 24-25. Sec., Dr. H. E. Jervey, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Rapid City, August 12-13. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TENNESSEE:* *Examination.* Memphis, Madison and Dunlap, June 11-12; Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 23-25. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 9-11. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VERMONT: *Examination.* Burlington, June 19-21. *Reciprocity.* Burlington, June 19. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Examination.* Richmond, June 12-14. *Reciprocity.* Richmond, June 11. Address: Board of Medical Examiners, 631 First St., S. W., Roanoke.

WASHINGTON:* *Examination.* Seattle, July 14-16. Administrator, Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination and Reciprocity.* Charleston, July 14-16. Sec., Dr. N. H. Dyer, State Office Bldg., No. 5, Charleston.

WISCONSIN:* *Examination.* Milwaukee, July 8-10. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, Oct. 6. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

HAWAII: *Examination.* Honolulu, July 14-15. Sec., Dr. I. L. Tilden, 1029 Kapiolani St., Honolulu.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* Juneau, Nov. 4. Sec., Dr. R. Harrison Leer, Room 204, Alaska Office Bldg., Juneau.

ARIZONA: *Examination.* Tucson, June 17. *Reciprocity.* Tucson, June 27. Sec., Dr. Herman E. Bateman, University of Arizona, Tucson.

ARKANSAS: *Examination.* Little Rock, Oct. 6-7. Sec., Dr. S. C. Dellinger, Zoology Department, University of Arkansas, Fayetteville.

COLORADO: *Examination and Reciprocity.* Denver, Sept. 3-4. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

CONNECTICUT: *Examination and Endorsement.* New Haven, June 14. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

IOWA: *Examination.* Des Moines, July 8. *Reciprocity.* Des Moines, July 7. Sec., Dr. Elmer W. Hertel, Waverly.

MICHIGAN: *Examination.* Ann Arbor and Detroit, Oct. 10-11. Sec., Mrs. Anne Baker, 116 Stevens T. Mason Bldg., W. Michigan Ave., Lansing 15.

NEW MEXICO: *Examination.* Santa Fe, July 20. *Reciprocity.* Santa Fe, June 26. Sec., Mrs. M. Cantrell, P. O. Box 1522, Santa Fe.

OKLAHOMA: *Examination and Reciprocity.* Oklahoma City, Sept. 26-27. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, June 7. Sec., Dr. Earl M. Pallett, Box 5175, Eugene.

TENNESSEE: *Examination.* Memphis, July 1-2. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

TEXAS: *Examination.* October. Certificates issued by reciprocity and waiver on the first and fifteenth of each month. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WISCONSIN: *Examination. Madison,* Sept. 19. Sec., Mr. William H. Barber, 621 Ransom St., Ripon.

*Basic Science Certificate required.

GOVERNMENT SERVICES

AIR FORCE

Consultants Visit Medical Installations.—Three national consultants to the surgeon general recently visited Air Force medical installations in Europe and in the Pacific. They rendered advice on problem cases in their specialties and conducted lectures and teaching sessions at medical installations. Dr. Clair M. Kos, professor of otolaryngology, State University of Iowa, visited installations in Japan, Korea, Okinawa, Taiwan, Hawaii, and the Philippine Islands. Dr. Carlos G. deGutierrez-Mahoney, neurosurgeon at St. Vincent's Hospital in New York City, and Dr. Frank E. Stinchfield, director, orthopedic service, Columbia-Presbyterian Medical Center, New York City, visited installations in Germany, France, Tripoli, Morocco, and England.

New Hospital in Indiana.—A U. S. Air Force Hospital at Bunker Hill Air Force Base, Peru, Ind., was completed on Jan. 30. This 50-bed hospital on a 100-bed chassis is a single story, air-conditioned structure of concrete, stone, and steel, with private and semiprivate rooms, four-bed and eight-bed wards, obstetric and gynecologic service, surgical service, laboratory, pharmacy, outpatient clinics, and dental clinic. Oxygen is piped throughout the wards and rooms. Patients may choose one of four radio programs by plugging speakers or headsets into the wall next to their beds.

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PUBLIC HEALTH SERVICE

First National Conference on Air Pollution.—Appointment of a committee to help plan a national conference on air pollution has been announced by the surgeon general. The national conference, first of its kind, will be held in Washington, D. C., Nov. 18 to 20, and will involve a full-scale review of current knowledge about the causes and effects of community air pollution, Dr. Burney said. The groups represented on the committee are:

Air Pollution Control Association
American Chemical Society
American Industrial Hygiene Association
American Iron and Steel Institute
American Medical Association
American Meteorological Society
American Municipal Association
American Petroleum Institute
American Public Health Association
Association of State and Territorial Health Officers
Automobile Manufacturers Association
Council of State Governments
Edison Electric Institute
Engineers Joint Council
Interdepartmental Committee on Air Pollution
Manufacturing Chemists' Association
National Advisory Committee on Community Air Pollution
National Coal Association

April Award for Research.—Research grants and fellowships totaling $5,725,219 were awarded during the month of April by the National Institutes of Health. Scientists and institutions throughout the nation received 334 research grants totaling $5,066,831. Sixty per cent of this amount supported research in the neurological diseases and mental health fields. The grants were made to 165 institutions in 38 states, the District of Columbia, 2 territories, and 5 foreign countries. The research fellowships were awarded to 149 individuals for study in 79 institutions in 27 states, the District of Columbia, and 8 foreign countries.

Twenty U. S. scientists were awarded fellowships for study abroad, while six scientists from other countries will receive research training at medical research centers in the United States of their own selection. (The six fellowships to scientists from other countries included in the April listing are among a group of 13 previously announced April 25.) Research grants are awarded to nonfederal research institutions for the support of research projects in the health sciences. Research fellowships support predoctoral and postdoctoral individuals interested in obtaining appropriate training for a research career.

Grant for Research on Aging.—The Public Health Service has made a grant of $417,939 to the Albert Einstein College of Medicine of Yeshiva University, New York City, for research on the medical and biological aspects of aging. Work to be carried on under the new grant, announced by the surgeon general during a ceremony at the university, will include (1) studies of changes that occur with age in the circulatory, nervous, and respiratory systems; (2) research training through 10 post-doctoral fellowships; each fellow to work with scientists in the new research unit, or with other faculty members engaged in research on aging; and (3) teaching, through the facility of a 90-bed ward service at the neighboring Van Etten Hospital to be established in cooperation with the city of New York.

The National Advisory Heart, Mental Health, and Arthritis and Metabolic Disease Councils recommended the grant. Although the Albert Einstein College of Medicine now has a research program on aging, the Public Health Service grant will establish a distinctly new program which will be supervised by the college's committee on gerontology.

This is the second grant in the Public Health Service's new program to encourage comprehensive research in the field of aging. The program is administered by the Public Health Service's Center for Aging Research, established in 1956, at the National Institutes of Health, Bethesda, Md., under the direction of Dr. G. Halsey Hunt. The first grant was awarded to Duke University, Durham, N. C., in August, 1957.

DEATHS

Alexander, Jewell Clyde, Livingston, Texas; University of Texas School of Medicine, Galveston, 1918; specialist certified by the American Board of Urology; member of the Texas State Medical Association and the American Urological Association; practiced in Houston, where he was professor of clinical urology at Baylor University College of Medicine; president of the Polk County Medical Society; veteran of World Wars I and II; member of the staffs of the St. Luke's Episcopal and Memorial hospitals in Houston; died March 23, aged 66.

Bolend, Rex George ✱ Little Rock, Ark.; St. Louis University School of Medicine, 1911; specialist certified by the American Board of Urology; member of the Oklahoma State Medical Association and the American Urological Association; veteran of World Wars I and II; at one time on the faculty of the University of Oklahoma School of Medicine in Oklahoma City; associated with the Veterans Administration Hospital; died in the Veterans Administration Hospital at Biloxi, Miss., March 23, aged 70.

Bolyn, Robert Talliaferro, Dallas, Texas; University of the South Medical Department, Sewanee, Tenn., 1901; died March 25, aged 84, of coronary occlusion.

Borders, Arthur Berry, Fort Worth, Texas; Meharry Medical College, Nashville, Tenn., 1917; died March 9, aged 69, of a self-inflicted gunshot wound.

Brantley, Thomas Boykin, Hilltonia, Ga.; University of Georgia Medical Department, Augusta, 1912; died in the Central of Georgia Railway Hospital, Savannah, March 24, aged 75.

Brumfield, Daniel Clyde, Darrow, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1900; member of the Louisiana State Medical Society; for many years Ascension Parish coroner; died in the Baton Rouge (La.) General Hospital March 23, aged 87, of acute pyelonephritis with abscesses, bilateral nephrolithiasis, subacute myelogenous leukemia, and injuries received in a fall.

Davis, William Cole, Lexington, Va.; University of Maryland School of Medicine, Baltimore, 1908; specialist certified by the American Board of Psychiatry and Neurology; veteran of World War I; resigned from the regular Army in 1920; commissioned a colonel and served as post surgeon at the Virginia Military Institute during World War II; formerly associated with the Norristown (Pa.) State Hospital; died in Caracas, Venezuela, Feb. 23, aged 75, of cancer and pneumonia.

Erwin, John Joseph ✱ Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1920; specialist certified by the American Board of Obstetrics and Gynecology; chief of obstetrics at Mercy Hospital; on the staffs of Hospital for Women and Bon Secours Hospital; died March 14, aged 65, of arteriosclerotic cardiovascular disease.

Farrall, Byron Huntley, Groton, Mass.; Boston University School of Medicine, 1926; veteran of World War I; died in the Community Memorial Hospital, Ayer, March 14, aged 60, of coronary disease.

Foley, Sydney Ira ✱ Flint, Mich.; M.B., 1914, and M.D., 1919, Queens University Faculty of Medicine, Kingston, Ontario, Canada; specialist certified by the American Board of Radiology, Inc.; member of the Radiological Society of North America and the American College of Radiology; served overseas as a captain in the Canadian Army during World War I; on the staff of St. Joseph Hospital, where he died March 12, aged 66, of cancer.

Freeman, David Barnard ✱ Moline, Ill.; State University of Iowa College of Medicine, Iowa City, 1910; fellow of the American College of Surgeons; member of the Aero Medical Association; past-president of the Rock Island County Medical Society; veteran of World War I; on the staffs of the St. Anthony's Hospital in Rockford and the Moline Public Hospital and the Lutheran Hospital, where he died March 13, aged 71, of pyloric obstruction secondary to carcinoma of the pancreas.

Fullerton, Oscar Lewis ✱ Redding, Iowa; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1902; died Feb. 12, aged 81, of heart disease.

Gerlough, Robert Jacob ✱ Menlo Park, Calif.; The General Medical College, Chicago, 1924; died in Palo Alto March 23, aged 65.

Griffis, Lawrence Glenn, Kalispell, Mont.; Indiana University School of Medicine, Indianapolis, 1910; an associate member of the American Medical Association; veteran of World War I; died March 15, aged 70.

Haldy, Walter Alfred ✱ Brunswick, Ohio; Western Reserve University Medical Department, Cleveland, 1902; died in Millersburg March 22, aged 79.

✱ Indicates Member of the American Medical Association.

Hamilton, Gordon Battelle, San Francisco; University of the South Medical Department, Sewanee, Tenn., 1905; College of Physicians and Surgeons, Boston, 1906; veteran of World War I; served with the city health department and as health officer of Contra Costa County; died March 19, aged 81, of coronary occlusion.

Hansen, Arthur Franklin ✦ Borger, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1925; past-president of the Hutchinson County Medical Society; served as a member of the board of directors of Panhandle State Bank; veteran of World War I; president of the staff of the North Plains Hospital, where he died March 16, aged 61, of nephritis and uremia.

Heald, John Emerson, Glendale, Calif.; American Medical Missionary College, Battle Creek, Mich., and Chicago, 1903; served as medical director of the Kansas Sanitarium in Wichita; formerly associated with the Battle Creek (Mich.) Sanitarium; died in the Glendale Sanitarium and Hospital March 13, aged 77, of coronary thrombosis.

Heineck, Aime Paul, Chicago; Northwestern University Medical School, Chicago, 1896; at one time on the faculty of his alma mater; served on the staffs of the Walther Memorial, Passavant Memorial, and Jackson Park hospitals; from July, 1913, to 1927 consulting editor in general surgery of the staff of the *International Abstracts of Surgery, Gynecology and Obstetrics;* died in St. Luke's Hospital April 8, aged 88, of cancer of the bladder and arteriosclerosis.

Hengstenberg, Hugh Herbert ✦ Madeira, Ohio; University of Cincinnati College of Medicine, 1925; member of the staffs of St. Elizabeth Hospital in Covington, Ky., Speers Memorial Hospital in Dayton, Ky., Good Samaritan, Bethesda, and Deaconess hospitals in Cincinnati; for many years company physician for the Cincinnati Gas and Electric Company; died in the Good Samaritan Hospital, Cincinnati, March 27, aged 57, of injuries received in an automobile accident.

Hobbs, Clarence Lowell, Collinsville, Ill.; St. Louis College of Physicians and Surgeons, 1922; Kansas City (Mo.) College of Medicine and Surgery, 1922; member of the Missouri State Medical Association; died in the Missouri Baptist Hospital, St. Louis, March 23, aged 73, of arteriosclerotic heart disease and cancer of the prostate.

Hufford, Clarence Elton ✦ Toledo, Ohio; born in Perrysburg, Ohio, Feb. 9, 1893; Western Reserve University School of Medicine, Cleveland, 1920; specialist certified by the American Board of Radiology; fellow of the American College of Physicians; past-president and secretary of the Northwestern Ohio Medical Association; past-president of the Ohio State Radiology Society, Academy of Medicine of Toledo and Lucas County, Radiological Society of North America, Ohio Division of the American Cancer Society, and the Toledo Public Health Association; member of the American Roentgen Ray Society, American College of Radiology, and the American Radium Society; in 1941 received a certificate of merit from the American Medical Association for his exhibit on bone tumors; for many years associated with St. Vincent's Hospital; died in the Indian River Hospital, Vero Beach, Fla., March 25, aged 65, of coronary occlusion.

Jinks, Clifford Herrmann ✦ Indianapolis; Indiana University School of Medicine, Indianapolis, 1924; served overseas during Warld War I; on the staffs of St. Vincent's and Methodist hospitals; died March 14, aged 61, of glioblastoma and cerebral anoxia.

Kaufman, Alexander Spencer, Philadelphia; born in Quincy, Ill., Oct. 21, 1882; Jefferson Medical College of Philadelphia, 1904; clinical professor of otology at his alma mater; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; an associate member of the American Medical Association; a member of the board of trustees of the National Agricultural College, Farm School, Pa.; on the courtesy staff of the Germantown Hospital and on the staffs of the Jefferson Hospital and the Northern Division of the Einstein Center, where he died March 30, aged 75, of ruptured aortic aneurysm and atherosclerosis of the aorta.

Kolb, Harrison John ✦ Oakland, Calif.; University of California School of Medicine, San Francisco, 1932; member of the staffs of Providence and Herrick hospitals and Peralta Hospital, where he died March 20, aged 52, of hemorrhage from esophageal varices and cirrhosis of the liver.

Kotkis, Alexander Joseph ✦ St. Louis; born in Gilberton, Pa., Sept. 11, 1895; St. Louis University School of Medicine, 1921; assistant professor of clinical medicine at his alma mater, where he was physician for athletic teams for a number of years; specialist certified by the American Board of Physical Medicine and Rehabilitation; member of the American Society of Physical Medicine and Rehabilitation; veteran of World War I; at one time served as boxing physician for the Missouri State Athletic Commission; since 1932 physical therapist at St. Mary's Group of Hospitals; died in Mount St. Rose Hospital March 23, aged 62.

Koven, Abraham ✦ Detroit; Detroit College of Medicine and Surgery, 1915; member of the American Academy of General Practice; for many years

diagnostician for the city health department; on the staff of the Detroit Memorial Hospital; died in the University Hospital, Ann Arbor, March 16, aged 63, of cancer.

Lamothe, Frank Eugene ✦ New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1908; on the consulting staff of Southern Baptist Hospital, where he died March 19, aged 74, of enterocolitis.

La Rue, Raymond T. ✦ Wilmington, Del.; Temple University School of Medicine, Philadelphia, 1920; associated with Delaware, St. Francis, and Delaware State hospitals; died March 17, aged 62, of heart disease.

Leden, Peter Paul ✦ Chicago; Schlesische Friedrich–Wilhelms–Universität Medizinische Fakultät, Breslau, Prussia, 1913; assistant clinical professor of otorhinolaryngology at Stritch School of Medicine of Loyola University; on the staff of St. Francis Hospital in Evanston, Ill., where he died March 31, aged 71, of myocardial infarction.

Loub, Martin Francis, Colorado Springs, Colo.; Colorado School of Medicine, Boulder, 1906; died March 15, aged 81, of bronchopneumonia.

Lynn, Frank M. ✦ Peru, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1894; formerly member of the city board of health, serving as secretary for eight years; served as city health officer; on the staff of the Dukes-Miami County Hospital; died March 17, aged 88, of uremia and heart disease.

McEwan, John Howard ✦ Bay City, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1913; member of the American Academy of General Practice; veteran of World War I; died in the Mercy Hospital March 14, aged 68.

McNemar, Oscar Harrison, Millersville, Md.; Maryland Medical College, Baltimore, 1903; formerly associated with the Veterans Administration hospital in Rutland Heights, Mass., and Castle Point, N. Y.; died March 21, aged 85, of heart disease.

McPherson, Garland, Hillsboro, Texas; University of Tennessee College of Medicine, Memphis, 1934; member of the Texas Medical Association; veteran of World War II; served as president and vice-president of the Hill County Medical Society; died March 17, aged 49, of a gunshot wound in the head.

Maxfield, James Robert Sr. ✦ Dallas, Texas; Fort Worth School of Medicine, Medical Department of Texas Christian University, 1901; past-president of the Van Zandt County Medical Society; received a selective service certificate of merit for his services during World War II; died March 20, aged 86, of cancer of the rectum with metastasis to the liver.

Moench, L. Mary ✦ White Plains, N. Y.; Johns Hopkins University School of Medicine, Baltimore, 1919; formerly associated with the Mayo Clinic in Rochester, Minn.; served as a member of the medical staff at Smith College in Northampton, Mass.; fellow of the American College of Physicians; served as instructor in medicine at Cornell University Medical College in New York City; associated with the New York Hospital and the White Plains Hospital, where she died March 27, aged 66, of cancer.

Moon, William Benjamin ✦ Crystal River, Fla.; Hospital College of Medicine, Louisville, Ky., 1897; veteran of World War I; state senator for three terms; died March 20, aged 87.

Morris, Frank Lincoln ✦ Cass City, Mich.; Detroit College of Medicine, 1910; served as a member of the school board and health officer; died March 17, aged 72, of coronary occlusion.

Morrissey, John Joseph Jr., Baltimore; Maryland Medical College, Baltimore, 1910; died March 29, aged 73, of carcinoma of the bladder.

Moses, Harry ✦ Palm Beach, Fla.; University of Virginia Department of Medicine, Charlottesville, 1908; fellow of the International College of Surgeons and the American College of Surgeons; associated with Good Samaritan Hospital and St. Mary's Hospital in West Palm Beach, where he died March 20, aged 76, of angina pectoris.

Newman, Adolph Jacob, Hinsdale, Ill.; Bennett Medical College, Chicago, 1910; retired from the Veterans Administration Aug. 31, 1955; for many years associated with the Veterans Administration Hospital in Hines, where he died April 4, aged 73, of coronary thrombosis.

Nill, Jacob Philip ✦ McKeesport, Pa.; University of Pittsburgh School of Medicine, 1925; veteran of World War II; on the staff of the McKeesport Hospital; died March 22, aged 59, of acute coronary occlusion.

Nutt, John Budd ✦ Williamsport, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1911; fellow of the American College of Surgeons; past-president of the Lycoming County Medical Society; veteran of World War I; associated with the Williamsport Hospital; died March 19, aged 73.

Ostrom, Frank Ward, Eaton, N. Y.; Hahnemann Medical College and Hospital of Philadelphia, 1904; died March 3, aged 75, of chronic myocarditis and congestive heart failure.

Peacock, Cassius Lee, New Orleans; Emory University School of Medicine, Atlanta, 1916; member of the Louisiana State Medical Society, of which he was formerly vice-president, and the American Urological Association; member of the House of

Delegates of the American Medical Association from 1944 to 1946; on the staff of the Southern Baptist Hospital; died March 16, aged 71.

Porter, Steven Alfred ✦ Okanogan, Wash.; University of Nebraska College of Medicine, Omaha, 1929; associated with St. Martin's hospital, Tonasket; died in Seattle March 2, aged 53, of myocardial infarction.

Raiguel, George Earle, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1902; died March 29, aged 77.

Ramsey, Rolla Benjamin, Richmond, Ind; Eclectic College of Physicians and Surgeons, Indianapolis, 1893; veteran of World War I; died March 19, aged 89, of arteriosclerotic heart disease.

Ray, William Burton Getty, Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1900; specialist certified by the American Board of Radiology; an associate member of the American Medical Association; member of the American Roentgen Ray Society, Radiological Society of North America, and the American College of Radiology; veteran of the Spanish-American War and World War I; associated with the Allegheny General Hospital, where he died March 21, aged 85, of carcinoma of the pancreas.

Rieke, Arthur George, San Francisco; University of Illinois College of Medicine, Chicago, 1918; served as assistant superintendent of the San Francisco Hospital; died in Blairstown, Iowa, Feb. 22, aged 71.

Robinson, Louis Henry ✦ Newark, N. J.; Long Island College Hospital, Brooklyn, 1906; died in Miami Beach, Fla., March 21, aged 75, of coronary disease and a cerebral accident.

Rubin, Harry, Kilgore, Texas; University of Pennsylvania School of Medicine, Philadelphia, 1912; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; veteran of World Wars I and II; formerly associated with the Veterans Administration hospitals at Augusta, Ga., Gulfport, Miss., Palo Alto, Calif., American Lake, Wash., and Waco, Texas; died in the Veterans Administration Hospital, Dallas, Texas, March 18, aged 67, of lobar pneumonia.

Rundell, William Kennard, Wichita Falls, Texas; Baylor University College of Medicine, Dallas, 1935; died in the Wichita General Hospital March 11, aged 48, of cerebral hemorrhage.

Sabin, George Millar ✦ Burlington, Vt.; University of Vermont College of Medicine, Burlington, 1900; professor emeritus of clinical surgery at his alma mater; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; veteran of World War I; on the staffs of the Porter Memorial Hospital in Middlebury and the Fanny Allen, Mary Fletcher, and Bishop de Goesbriand hospitals; died March 21, aged 84.

Sayler, John Milton, Dayton, Ohio; Starling Medical College, Columbus, 1903; chief medical examiner for the Baltimore and Ohio Railroad in Cleveland for many years; died March 18, aged 79.

Schaeffer, Jacob H., Cridersville, Ohio; Medical College of Ohio, Cincinnati, 1891; served on the staffs of the Memorial and St. Rita's hospitals in Lima; died in St. Mary's, March 19, aged 93.

Schnur, Howard Lee ✦ Houston, Texas; Columbia University College of Physicians and Surgeons, New York City, 1949; certified by the National Board of Medical Examiners; service member of the American Medical Association; veteran of World War II; assistant chief, department of physical medicine and rehabilitation, Veterans Administration Hospital, where he died March 22, aged 40, of cerebral hemorrhage and acute leukemia.

Selman, Willis Lee, San Antonio, Texas; (licensed in Texas, under the Act of 1907); died March 13, aged 83.

Skillin, Waldo Thompson, South Portland, Maine; Medical School of Maine, Portland, 1914; served as chairman of the board of education, health officer, and as a medical examiner; died March 18, aged 68.

Snodgrass, Thomas Joseph ✦ Janesville, Wis.; University of Minnesota Medical School, Minneapolis, 1916; specialist certified by the American Board of Surgery; veteran of World War I; member and past-president of the Western Surgical Association; member of the American Trudeau Society; fellow of the American College of Surgeons; a founder and past-president of the Wisconsin Surgical Society; formerly member of the city council; on the staff of the Mercy Hospital; died April 7, aged 66, of injuries received in an automobile accident.

Stevens, Charles Elmer ✦ Ironwood, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1910; served as city health officer; chief of staff, Grandview Hospital; associated with Divine Infant Hospital in Wakefield; died in the F. A. Bell Memorial Hospital, Ishpeming, March 4, aged 74, of bronchogenic carcinoma.

St. Onge, Joseph Abel ✦ Sioux City, Iowa; Sioux City College of Medicine, 1907; on the staff of St. Vincent's Hospital; died March 17, aged 76, of coronary occlusion.

Tannenbaum, Israel Samuel ✦ Worcester, Mass.; Kansas City (Mo.) University of Physicians and Surgeons, 1929; served as medical examiner for the Boston Mutual Life Insurance Company; for many years on the courtesy staff of the St. Vincent Hospital; died in Miami, Fla., March 20, aged 55, of acute pulmonary edema and arteriosclerotic heart disease.

Terry, George Hiram Blakeslee, Asheville, N. C.; Jefferson Medical College of Philadelphia, 1895; veteran of World War I; served with the Veterans Administration; died March 4, aged 87, of heart disease.

Tiffany, William James, New York City; born in Groton, N. Y., July 29, 1882; Columbia University College of Physicians and Surgeons, New York City, 1905; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association and the Association for Research in Nervous and Mental Diseases; state commissioner for mental hygiene from 1937 to 1943; entered the state hospital service in 1906, attached to Binghamton (N. Y.) State Hospital and Manhattan State Hospital in New York City; formerly superintendent of the Kings Park (N. Y.) State Hospital and the Pilgrim State Hospital in Brentwood; died in the Neurological Institute of the Columbia–Presbyterian Medical Center March 28, aged 75, of coronary thrombosis.

Treusch, Herbert Louis ✦ Washington, D. C.; Emory University School of Medicine, Atlanta, 1925; service member of the American Medical Association; served as vice-president of the American Physicians' Art Association; formerly practiced in Atlanta, where he was associated with the Crawford W. Long Memorial Hospital; medical officer of the Veterans Administration Board of Veterans Appeals; died March 25, aged 57.

Turnage, Johnson Lee, Fort Walton, Fla.; Tulane University School of Medicine, New Orleans, 1942; certified by the National Board of Medical Examiners; veteran of World War II; public health director; died March 19, aged 43, of acute myocardial infarction.

Ullrich, Henry Franz ✦ Baltimore; born in Baltimore Nov. 17, 1903; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1929; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow and member of the board of governors of the American College of Surgeons; associate professor of orthopedic surgery at his alma mater; veteran of World War II; associated with the Franklin Square, Mercy, St. Joseph's, Maryland General, Bon Secours, University, Union Memorial, Lutheran, and St. Agnes hospitals, and Church Home and Hospital; died in the University Hospital March 24, aged 54, of lymphosarcoma.

Van Lengen, Nicholas Warner ✦ Syracuse, N. Y.; Syracuse University College of Medicine, 1909; one of the founders and member of the board of directors of Peoples Hospital, where he died March 16, aged 71, of acute myocardial infarction.

Verity, Walter, Chicago; Rush Medical College, Chicago, 1910; veteran of World War I; served on the staffs of the Woodlawn Hospital and the City of Chicago Municipal Tuberculosis Sanitarium; died in the Albert Merritt Billings Hospital April 1, aged 83, of acute myocardial infarction.

Walker, Roger Venning Jr. ✦ Detroit; Wayne University College of Medicine, Detroit, 1951; instructor of surgery at his alma mater; associated with Detroit Memorial and Receiving hospitals; died in the Henry Ford hospital March 19, aged 32.

Wesson, Paul D., Memphis, Tenn.; St. Louis College of Physicians and Surgeons, 1922; died March 21, aged 70, of pneumonia.

Westby, Magnus ✦ Madison, Minn.; University of Minnesota Medical School, Minneapolis, 1927; member of the American Academy of General Practice; president of the state board of medical examiners; twice mayor of Madison; on the staff of the Madison Hospital; died in Santa Ana March 13, aged 58, of coronary occlusion.

Wilhite, David Walter Jr. ✦ La Mesa, Calif.; University of Southern California School of Medicine, Los Angeles, 1949; associated with the Paradise Valley Sanitarium and Hospital, National City; died March 9, aged 32, of an overdose of barbiturates, self administered.

Wright, Thew, Buffalo, N. Y.; born in Boston June 19, 1877; University of Buffalo School of Medicine, 1903; professor of surgery emeritus at his alma mater; an associate member of the American Medical Association; member of the Medical Society of the State of New York and the American Association of Obstetricians and Gynecologists; fellow of the International College of Surgeons and the American College of Surgeons; member of the founders group of the American Board of Surgery; veteran of World War I; formerly member of the city board of health; served on the staff of the Buffalo General Hospital; died in the Veterans Administration Hospital March 20, aged 81, of cerebral thrombosis.

Wyman, Frank Bertram ✦ Seattle; Northwestern University Medical School, Chicago, 1950; member of the American Academy of General Practice; died in the Maynard Hospital March 9, aged 34, of coronary artery occlusion.

FOREIGN LETTERS

FRANCE

Blood Urea Levels.—Since Widal analyzed the successive steps of progressive azotemia in the course of chronic nephropathy, many physicians have relied on serum urea levels to detect renal insufficiency. Hamburger and Masson (*La presse medicale* **66**:499, 1958) studied 150 unselected patients from a nephrology consultation unit. They compared the urea level with the values of the urea clearance and the glomerular clearance and found 50 mg. of urea per 100 ml. of serum to be an unreliable guide to kidney function in patients who were not examined under strict basal conditions. One may find the concentration of urea to be less than 50 mg. per 100 ml. in patients in whom more than a half of the functional value of the kidneys was already lost, and one may find levels above 50 mg. per 100 ml. in patients whose renal function was normal.

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INDIA

Thoracic Injuries.—Anand and Singh (*Indian Journal of Surgery*, vol. 20, February, 1958) stated that fractures of the ribs are the commonest type of thoracic injuries in civilian practice. About 15% of patients with closed thoracic injuries, most of whom are run over by automobiles, die. The stove-in chest is almost always fatal unless prompt and proper treatment is given. The authors reported a series of 75 cases of closed thoracic injuries in which 10 patients had paradoxical respiration and 5 had stove-in chests. The complications noticed in these cases were pulmonary edema, hemothorax, tension pneumothorax, diaphragmatic hernia, and acute dilatation of the stomach. In treating ordinary fractures of the ribs, relief of pain is all that is required, and this was provided by using intercostal or paravertebral block. Five patients had blood in the pleural cavity; it was aspirated from three of these. No patient required decortication. The four patients with tension pneumothorax were treated by intercostal aspiration with a needle connected to a tube under water seal. In treating patients with stove-in chests, the surgeon may be confronted with paradoxical respirations, severe pain from fractured ribs, and excessive tracheobronchial secretion.

Of the five such patients in this series only two required an operation to stabilize the chest; both recovered. Fixation of the ribs was obtained with silk or stainless steel wire sutures without any external traction. The other three patients died, one an hour after admission due to an associated fracture of the skull, one 10 hours after admission of an associated tension pneumothorax on the same side and massive hemothorax on the opposite side, and the third 3 days after admission of pulmonary edema and acute dilatation of the stomach. Intercostal or paravertebral block was used to relieve the pain. An intravenous drip of procaine in saline solution was given if this failed. Shock was treated by transfusion of blood, dextran, and other fluids. The authors did not use tracheotomy to restore normal respiratory movements in any of these patients, but others have found an early tracheotomy to be a lifesaving measure in many patients with crushing thoracic injuries as it reduces paradoxical movements, alleviates pain by decreasing movements of the fractured ribs, and provides an easy method for aspirating the tracheobronchial tree without the need for a bronchoscope in patients with pulmonary edema.

Acetazolamide in Ophthalmology.—J. M. Pahwa (*Indian Journal Medical Sciences*, vol. 12, Jan., 1958) stated that acetazolamide, a powerful carbonic anhydrase inhibitor, lowers intraocular pressure. It has therefore been used in the treatment of glaucoma. Although the exact mechanism of its action is not known, it is believed to diminish the production of aqueous humor. It reduces the aqueous inflow by lowering the aqueous electrolytic concentration and osmotic pressure. The author tried this drug in a series of 100 patients with acute and chronic glaucoma. Complications were few, but in one patient there was epistaxis. Results were good in those with acute congestive glaucoma and secondary glaucoma due to coughing, iritis, or trauma. Two patients with chronic glaucoma were well controlled for over eight months, but, in general, the results were uncertain in chronic glaucoma. The drug was found useful in postoperative nonformation of the anterior chamber after intraocular operations where no leak could be detected, particularly in patients with detachment of the choroid. It was also of use after keratoplasty, where it helped in the prevention of noninflammatory edema of the cornea. The best results were obtained in patients with acute congestive glaucoma, especially when combined with miotics.

Anesthetic Action of Antihistaminics.—R. Goswami and co-workers (*Indian Journal of Medical Sciences*, vol. 12, February, 1958) stated that most antihistaminics, besides having a sedative action,

The items in these letters are contributed by regular correspondents in the various foreign countries.

possess local anesthetic activity on topical application in certain skin irritations. They investigated the local anesthetic action of promethazine hydrochloride and pyrilamine maleate and evaluated their potency in relation to procaine hydrochloride which was taken as the standard. Studies of the local anesthetic action of these two antihistaminics carried out on guinea pigs showed that promethazine and pyrilamine in 0.25, 0.5, and 1% M/15 phosphate buffer solution did not produce surface anesthesia of the cornea. Intradermal injections of 0.2 ml. of solutions of the antihistaminics in the strengths mentioned did produce local anesthesia, the degree and duration of which were more potent and lasting than those of solutions of procaine hydrochloride of the same concentration and quantity. This was even more marked in human volunteers. Promethazine and pyrilamine are, respectively, 2 and 1.7 times more potent than procaine hydrochloride in this respect. Intradermal injections of 0.2 ml. of 0.5% solutions of promethazine and procaine given together produced complete local anesthesia for 25 minutes. This effect is more potent and lasting than that produced by a 0.5% and even of a 1% solution of either drug alone. A total dose of up to 50 mg. of promethazine could be safely injected subcutaneously without the likelihood of any serious toxic reaction. It can also be used in combination with procaine in concentrations lower than usually required for procaine anesthesia.

Hypothyroidism.—Manchanda and Sharma (*Indian J. Pediat.* **25**:119 [Jan.] 1958) reported a series of 12 patients with hypothyroidism. Eight had not been given a diagnosis, and two were being treated for marasmus and rickets. These patients showed a stunted growth, marked apathy, constipation, dry skin, rough lusterless hair, umbilical hernia, large tongue, and marked mental retardation, but, whereas the physical and mental activities were constantly below par, sexual development was variable and presented interesting differences. Thus a 20-year-old man had fully developed secondary sex characteristics while another of the same age showed absence of these characteristics. The same lack of secondary sexual characters was seen in two women aged 18 and 22 years respectively. Seven of the 12 patients were between the ages of 2 and 10 years, and the rest were between 11 and 22. Stunted growth and characteristic skeletal changes of retarded growth were observed in the roentgenograms of all the patients. The blood cholesterol level was raised to over 200 mg. per 100 cc. in only 5. All showed anemia, the hemoglobin value varying from 3.5 to 11.9 Gm. per 100 cc. The anemia was microcytic in three, normocytic in eight, and macrocytic in one. Electrocardiograms in 11 cases showed the characteristic poor voltage pattern in seven. Basal metabolic rate estimations were made in two cases only and gave low values. There was no family history of goiter in any of these cases. Except for one patient whose mother lived in a goitrous region for the first six months of pregnancy, all the patients came from nongoitrous districts. No antithyroid drugs had been taken by any of the mothers during pregnancy.

House Dust as a Respiratory Allergen.—L. M. Sanghvi and co-workers (*Journal of the Indian Medical Association*, vol. 30, April 1, 1958) investigated 100 patients with respiratory allergies of whom 55 had bronchial asthma, 23 had hay fever, 16 had allergic rhinitis, and 6 had allergic bronchitis. Nasal smears were examined, and intracutaneous skin testing was done with dust as well as pollen allergens. A positive reaction was considered significant only if either there was a history of attacks after exposure to dust or the patient showed a marked reaction on intracutaneous testing. Of the 100 patients, 79 gave a history of precipitation of symptoms on exposure to dust. Positive reactions to dust were obtained in 89 patients, including these 79 and 10 others. Of the 55 patients with asthma, 34 had perennial and 21 seasonal attacks. Of the 34 with perennial attacks 30 had symptoms on exposure to dust and 33 showed a positive skin reaction to the dust allergen. Of the 21 with seasonal asthma, symptoms were precipitated on exposure to dust in 14 and a positive skin reaction was obtained in 15. Of the 23 patients with hay fever 18 were sensitive to inhaling dust and gave a positive skin reaction. Of the 16 patients with allergic rhinitis 15 were sensitive to inhaling dust and gave a positive skin reaction. The same findings were observed in all six patients with allergic bronchitis. Of the 79 with positive history, 28 showed a positive skin reaction to pollen allergens also. Patients with seasonal allergy who gave positive reaction to dust invariably gave positive reaction to one or more other allergens. The results of hyposensitization treatment with subcutaneous injections of the dust extract in all sensitive patients were highly encouraging, there being a diminution of symptoms and an increased interval between attacks.

Tuberculosis.—The 14th Tuberculosis Workers' Conference was held in Madras early this year. Dr. P. V. Benjamin stated that the most important activity in the last three years was the country-wide survey of the incidence of tuberculosis by mass miniature radiography. This survey, although not yet completed, indicates that the incidence of tuberculosis varies from 7 to 30 per 1,000 population, males being more frequently affected than females. There was no marked difference in the incidence of the disease in villages, towns, and cities. There are now 23,000 beds for tuberculosis patients, but, although this is 17,000 more than were available 11 years ago, it represents only 1 bed for every 106 patients suffering from the disease. The number of tuberculosis clinics has increased from 103 in 1947 to 200. New training and demonstration centers have also been established. BCG vaccination is be-

ing used on an ever-increasing scale. A promising activity begun in recent years is domiciliary treatment under the supervision of clinics equipped with x-ray units and laboratories.

Medical Gases.—The system of coloring cylinders of medical gas in India did not correspond with that used in many other countries. As a result accidents occurred from mistakes in identification of gases by foreign physicians or by those trained overseas. The Government has therefore amended the Gas Cylinder Rules so that the color markings of these cylinders will conform with the international system.

Nutrition of School Children.—Nutritional surveys of school children by the State Nutritional Advisory Committee showed that the main deficiency was of vitamin A. Only a few children with riboflavin deficiency were seen, and the incidence of deficiency of vitamins C and D was not high. The incidence of dental caries was about 20%. Nearly 40% of those examined had a poor physique. In most places the intake of vegetables, especially green leafy vegetables, was inadequate. Except in the western districts where ghee was taken in small quantities, the fats and oils used were usually vanaspati and mustard oil. The intake of fats derived from animal sources was low. Seasonal fruits included bananas, papayas, guavas, and mangoes but the quantities taken were small. Milk, milk products, and meat were either absent from the diet or their intake was low. The diets of these children were characterized by high intake of cereals and low consumption of protective foods.

In view of these investigations, the State's Education Department is teaching nutritional principles in schools through lectures and visual aids and has a program of midday meals in practically all the secondary schools. Puffed rice, parched gram, sprouting gram, and seasonal fruits are distributed to school children. Intensive efforts are being made to educate and persuade the villagers to have small kitchen gardens to meet their requirements of green leafy vegetables. The intake of germinated pulses is being encouraged. In certain areas, school children between the ages of 5 and 12 are given potassium iodide as a prophylactic measure against endemic goiter for 10 days in spring and autumn.

PORTUGAL

Prefrontal Lobotomy.—Nunes da Costa (*Anais Portugueses de Psiquiatria*, Sept. 9, 1957) made a follow-up survey on 197 patients who had had prefrontal lobotomy. Most of these patients (130) were schizophrenic. The survey included interviews with members of the families and working associates. In relation to the course of the mental disease, the best results of lobotomy were obtained in psychosis, with spontaneous remission. Lobotomy can arrest, for a variable time, the development of the psychosis, especially in patients with spontaneous periodic remissions; but it can neither definitively arrest nor favorably modify the eventual course. Relapses are frequent, and they are attended by the usual symptoms. Analyzing the influence of lobotomy on the patients' personality, the author found (1) concerning the process of thinking: diminution or loss of "abstraction" and of the elaboration of thinking, superficiality of the thoughts, diminution or loss of imagination and the representative capacity, diminution of attention and memory, extraversion, diminution of the capacity of synthesis, alterations of perception, and poorer grasp of language; (2) concerning affectivity: diminution of the affective reaction, emotional flattening, loss of inhibitions, superficiality of contacts, and loss of interests; and (3) concerning activity: diminution of initiative and general activity and a tendency to akinesia. Lobotomy causes a diminution of the capacity of reaction of the organism to disease in general. Mortality is high among lobotomized patients. Hunger and pain lose their vital functions of alarm. If some improvement of the psychosis is obtained this must be weighed against the disadvantages.

UNITED KINGDOM

Serum Lipids in Diabetic Children.—It is generally considered that the serum lipoprotein level rises before the development of atheroma, and in diabetics there is a tendency for arterial disease to develop prematurely, leading to occlusive coronary disease, retinopathy, and nephropathy. Wolff and Salt (*Lancet* 1:707, 1958) studied the serum lipids and lipoproteins in 35 diabetic children, who, although showing no evidence of arterial disease, are almost certain candidates for its development. The mean levels of beta-lipoprotein, lipid, cholesterol, and esterified fatty acids in the serum were significantly higher in the children with blood sugar levels above 200 mg. per 100 ml. than in those with lower levels. As the blood sugar level rose so did that of the serum beta-lipoprotein. In three children with moderate or slight ketosis, whose diabetes had never been treated, the serum lipid level was high, the rise being mainly in the beta-lipoprotein fraction. After treatment with insulin, the fall in blood sugar level was accompanied by a corresponding fall in the serum beta-lipoprotein level. In two patients it was reduced to normal in one or two days.

One child, with long-standing diabetes, admitted in coma, had a high level of serum total lipid and beta-lipoprotein. She recovered, but gangrene and peripheral neuritis developed. The serum lipoprotein and blood sugar levels were still within normal limits several months later, although complications were still present. In this case the serum lipid abnormality preceded the development of arterial disease but remained reversible with insulin treatment. These observations supported the

view that a rise in the serum beta-lipoprotein level occurs when insufficient carbohydrate is available for metabolic needs, as in untreated diabetic hypoglycemia. The high levels of beta-lipoprotein and cholesterol in the serum of these children resembled those known to precede the development of atheroma in nondiabetic persons. Although the raised beta-lipoprotein level has not been proved to cause early arterial complications in these young diabetics, it is desirable to maintain in them a normal serum lipid level.

Side-Effects of Morphine.—Dr. Christie and coworkers (*British Medical Journal*, March 22, 1958) gave three series of volunteers (46 soldiers in the Australian Army, 58 female patients awaiting minor operations, and 28 students) certain drugs in combination with varying amounts of morphine, up to 30 mg. The most frequent side-effect of morphine was not respiratory depression but nausea and vomiting, the incidence of which may be as high as 30%. The onset of emesis may be delayed for seven hours. The nausea and vomiting may be completely controlled by the use of cyclizine. The central nervous system depression (narcosis) may be controlled with amiphenazole. Provided the sensitivity of the patient to small doses is first ascertained, morphine is not a dangerous drug. All the side-effects can now be controlled. Doses of morphine up to 200 mg. may be required to control chronic pain. The patient should not be denied the benefit of complete analgesia on the score of side-actions or addiction. The results of over 400 cases show such fears to be groundless when the appropriate antagonist is used.

Bronchitis Morbidity.—One way to increase production and reduce the cost of living would be to diminish the morbidity from chronic bronchitis according to *Medical Press* of March 22. Bronchitis caused the loss of more than 23 million working days in 1956. This total is sufficiently formidable to draw attention to the importance of this disease to the victim and to the community as a whole. How far smoking contributed was not known, but the fact that bronchitis was five times as common in men as in women paralleled to some extent the preponderance of bronchial carcinoma in men as compared to women. This suggested strongly that there, too, tobacco may be an important factor.

Bureaucracy.—Dr. Hale White, chairman of the Fellowship for Freedom in Medicine, speaking at the annual general meeting, said that there were 40,000 clerks and administrators in the Health Service, or more administrators than physicians. Each of these works a 38-hour week. Anything above this is called "overtime," a term quite incomprehensible to a professional man. At one hospital in London the administrative and clerical staff numbered less than 30 in 1948; today it is 160. The Guillebaud Committee, however, could not find "any large inflation of clerical or administrative staff at the present time." These nondoctors in the Health Service do not include nurses or personal secretaries; they are mostly clerks who spend their time recording the sort of information about patients that a general practitioner records in the ordinary course of his work without extra cost to the nation. Another large body spend their time collecting and rendering information to regional hospital boards and the Ministry. This is subsequently translated into statistics, which are out of date before they are compiled. A large proportion of this paper work is of no practical use.

Tuberculosis in Refugees.—The Joint Tuberculosis Council stated that about 7,000 of the 15,500 Hungarian refugees remaining in Britain have had roentgenograms of the chest and that the incidence of tuberculosis among those examined is 0.8%. This is two or three times the incidence of the disease found in British surveys. Among the remaining refugees there are probably still 50 to 100 active but undiagnosed cases of tuberculosis. The council considers that the refugees should have had roentgenograms on entry into the country and suggests that in any future emergency involving the sudden influx of refugees this should be done at the transit camps, where it should be explained that if tuberculosis is found the refugee will not be sent back home but will be treated free.

Chair of Anesthesiology.—The British Oxygen Company has provided $422,250 for the establishment of a new chair of anesthesiology at the Royal College of Surgeons, London. In spite of the advances being made in the subject this is the first chair of its kind in London. A laboratory for research in anesthesiology was opened at the college in 1957, and its director, Dr. Ronald F. Woolmer, will be the new professor. His department is financed entirely by funds from industry and not from the college. No conditions are imposed on the use of the money, which is administered by the Faculty of Anesthetists.

Conditioned Opinion.—Sir William Haley, former director-general of the B. B. C. (*The Times*, March 12, 1958) cited an example of the way emotion can pass for opinion. He told of a weekly index figure kept by the corporation during World War II showing what listeners had thought of programs as a whole. One week the rating was so bad that a mistake was suspected. No mistake was found nor was there any qualitative difference in the programs for that week. Someone noted that during the week in question, the failure of the paratroop drop on Arnhem had become fully known. This led the B. B. C. to compile a weekly graph of program appreciation

figures related to the main events of the war. They also graphed a morale index of the British nation. The two graphs were strikingly parallel. It was concluded that while public polls can tell us accurately what people think, they give us, as now conducted, no clue as to why they think it.

Advice on Marriage.—Advice on what a young couple want to know about marriage, from sex to income tax, is given by 37 specialists in the 1958 version of "Getting Married," published by the British Medical Association, and selling for about 20 cents. Dr. Harvey Flack in the foreword says that love may not conquer all, but just being in love makes a lot of problems fall into perspective. Professor Ashley Montagu, the American anthropologist, writes that a pretty or handsome face can conceal a pretty awful mess and not infrequently does. An ordinary face is often the appearance beneath which resides great strength and beauty of character. The idea of character should be substituted for physical attractiveness as a basis for marriage. On premarital intercourse he states: "Getting to know the other person emotionally and intellectually is vastly more important than getting to know them sexually. Indeed, sexual attraction is likely to obscure the judgment." Nagging is dealt with by another American contributor, Dr. Stanley R. Dean. He pins the fault of nagging on women, with the explanation that women, lacking the physical outlets of men to dissipate aggression, tend to resort to words and adds that even a brisk walk helps a lot. His recipe for a happy marriage is: "One in which the wife is a little bit blind and the husband a little bit deaf."

Six golden (economic) rules, given by Dr. Dick Glover, are: 1. Have some capital, or at least a steady income. 2. Live in a district where most of your neighbors have about the same incomes. 3. Tell your wife how much you earn. 4. Make your wife a regular allowance if possible. 5. Have a sense of proportion about spending. 6. Put away something for emergencies.

Dispute in Malta.—On March 12, the Malta branch of the British Medical Association asked the Association to mediate with the Maltese prime minister on a dispute which has arisen between the profession in Malta and the Maltese government. The dispute is a sequel to a previous one which culminated in the Maltese government inviting a medical services commission to review the medical service in Malta and make recommendations on its terms of employment. The commission's report was published in 1957. In last year's discussions between the Medical Officers Union of Malta and the Maltese government, the government indicated that it was not prepared to implement certain of the commission's recommendations. In particular it was not prepared to give the new advisory and executive board the powers recommended by the commission, and it refused the right to arbitration on terms and conditions of employment. It also refused to adopt the remuneration recommended in the commission's report, on the grounds that a further review of civil service remuneration was to be made.

On Feb. 26, the Medical Officers Union threatened a repetition of the collective resignation which had been organized a year previously. The Maltese Minister of Health then announced in the Legislative Assembly that the government would accept all resignations and that acceptance would imply immediate termination of service, and in that case the government would disallow physicians all government facilities, such as the use of hospitals and dispensaries. Further, all resigning medical officers occupying government quarters would be required to vacate them. Continuity of service with its accruing benefits and rights would be forfeited, and those wishing to rejoin government service at a future date would have to do so under a new contract and no consideration of past service would be taken. The Medical Officers Union countered this by announcing that its members would not resign from government service but that there would be a concerted cessation of government work. A service for emergency cases would be continued and patients would be allowed to attend physicians privately. No date was fixed for this action.

Cure for Smoking Habit.—A scheme for the treatment of smoking addicts on the lines of Alcoholics Anonymous has been initiated by the National Society of Non-Smokers, which aims at establishing a number of "smoking clinics" to provide medical and psychological treatment backed up by the effect on morale on contact with fellow sufferers and former addicts who have been cured of the habit. The first clinic opened in Liverpool in March, with sessions once a week, but it proved so popular that provision is being made for it to be open daily. A second clinic will be opened in London. Experimental meetings of smokers have been held in other cities with a view to establishing other clinics. Some smokers travel 70 miles to their nearest clinic in search of a cure. General psychotherapy is first given to groups of up to 12, followed by a personal interview with a physician. After a week or two the patient returns to the clinic to report progress. Most of the patients are 45 or more. One of them smokes 80 cigarettes a day at a cost of $15.50 a week.

Stuttering.—In view of the handicap which stuttering presents, Maxwell and Patterson (*Brit. M. J.* 1:873, 1958) investigated the action of meprobamate, which relieves anxiety and tension. Eighteen patients, severely affected by stuttering and defects in social adjustment, and who had previously

shown little response to speech therapy, were selected for treatment. They were seen at intervals of one week during active treatment and later at intervals of one month for a total period of eight months. They were given 400 mg. of meprobamate three times a day. An excellent result was obtained in six patients, a good result in eight, and little or no improvement in four. An excellent result was considered to be one in which the extent of improvement was such that speech difficulty appeared only during exceptional emotional tension. A good result was considered to be one in which subjective and objective improvement permitted satisfactory employment, with intermittent speech hesitancy. Inert control tablets were used in the treatment of eight patients, but only two claimed some subjective benefit. Meprobamate interrupts the vicious circle of tension, speech inhibition, and consequent anxiety in those who stutter, makes patients more accessible to speech therapy, and enables better results to be obtained in suitable cases than the application of standard methods over a longer period.

Cancer Statistics.—The General Register Office summarized cancer statistics for England and Wales from the beginning of the century to the present (McKenzie, A: Cancer Statistics for England and Wales, 1901 to 1955, Her Majesty's Stationery Office). In the last 20 years the total mortality from cancer of all sites increased for men at every age, but it decreased among middle-aged women. This difference between the two sexes is largely due to the much higher incidence of cancer of the lung in men. The commonest sites for cancer, causing death in the period 1950 to 1954 were, for men, lung (336 per million population), stomach (211), intestine (109), rectum (88), and prostate (74). For women the figures were breast (182), stomach (118), uterus (91), ovary (60), and intestine (6). About 1% of those dying of cancer were children under 15, and over half of these deaths were due to diseases of the blood-forming organs. There were regional differences in death rates from cancer. Thus in Wales the mortality from cancer of the esophagus was high, while that of cancer of the lung was low. The North of England had a high mortality from cancer of the stomach. The effect of industrialization on cancer of the lung was apparent, the incidence being higher in large industrial areas. On the other hand the death rates from cancer of the pancreas, kidney, and bladder were relatively higher in Southern England than elsewhere.

Press Not Admitted to Broadcasts.—The Council of the British Medical Association decided not to admit representatives of the lay press to the clinical demonstrations to be televised at the annual meeting of the Association in Birmingham. They will be admitted only during the televising of surgical operations. The council was asked to allow the press to be present during the whole program, but it rejected this request as it thought that only the most sensational aspects of the clinical cases were likely to be reported.

Food Poisoning due to Clostridium Welchii.—McNicol and McKillop (*Lancet* 1:787, 1958) reported an outbreak of food poisoning due to Clostridium welchii in a Glasgow hospital. Nine of 15 patients and a kitchen maid were affected after eating cold chicken. These patients were on a special light diet. Others in the same ward on ordinary diet were unaffected. The maid was taken ill after eating leftover chicken. Rectal swabs from all 16 persons were taken and nonhemolytic heat-resistant Cl. welchii isolated from 11. The identity of all the cultures was confirmed by demonstration of the fact that they produced Cl. welchii α-toxin and that was specifically neutralized by α-antitoxin. The clinical findings were typical. About eight hours after the precooked chicken was eaten, there was a brief illness characterized by colicky lower abdominal pain and watery diarrhea, without mucus, blood, or pus. Pyrexia was absent and systemic upset minimal.

Scotland's Health.—The Department of Health for Scotland reports that while the death rate was falling in all other groups, in men in the second half of life it was rising. This rise was not due to the increase in the average age of the population but to an increase in morbidity. The report states that at and beyond middle age there were few causes of death that did not affect men more than women. The chief cause of increased male mortality was the greater incidence of cardiovascular and pulmonary disease in aging men. If it were not for these illnesses the male death rate would be close to that of the female. The mortality of men aged 55 to 64 from all causes increased in Scotland in the last decade, yet in England and Wales it remained more or less stationary in this age group, although the rate in men over 65 increased. In women of 75 and over the death rate was fairly constant in the last decade and decreased in all other age groups. Infant mortality continued at a low rate. Deaths from tuberculosis were 13 per 100,000 population, compared with 66 10 years ago, but reported cases of tuberculosis increased from 5,915 in 1956 to 7,859 in 1957, not because of an absolute increase in the incidence of this disease but from improved case-finding with the help of mass roentgenography. In the 1957 drive 1,319,867, or about 20% of the population, were x-rayed. The chief cause of death after cardiovascular disease and cancer was accident. Bronchitis was the fifth on the list as the cause of death and was responsi-

ble for most absence from work. Influenza took its toll of 90 deaths in one week, although on the whole this condition was relatively benign over the year. The state of children's teeth caused some alarm. Dental examinations revealed that 20 to 30% of the teeth of children aged 12 were missing, decayed, or filled.

Cost of National Health Service.—The National Health Service, 10 years old this July, has proved far more expensive than was originally contemplated, even taking into account the rise in prices and the fact that people are living longer. The gross cost of the service has increased from 1,225 million dollars in 1949-1950 to 2,083 million dollars yearly. This is an increase of 70%. The expenditure represents 3.7% of the country's total income. The personnel employed in the health service has increased. In the last 10 years the number of nurses has gone up from 148,812 to 181,470, and medical and dental staff in the hospitals has increased from 11,940 to about 17,000. Administrative and clerical staff have expanded from 25,117 to 32,000. There are also 2,000 more general practitioners than 10 years ago. There has been an increase in the number of hospital beds, from 448,057 to 476,870, and 800,000 more inpatients were treated in the last year than in 1949. Outpatient attendances went up from 26 million a year to nearly 28 million, and free domiciliary specialist consultations from 129,500 to 265,000. Prescriptions increased from 202 million in 1949 to nearly 229 million and the number of dental treatments from 6,768,000 to 8,619,000. Only for false teeth and spectacles was there a decline.

The rise in cost of the health service is due to an increase in the services offered, rising prices including salaries and wages, a rise in the population, and an increase in the number of the aged, who need more medical attention than the young. An average of about $3 a week of health service funds are now spent on each family. Undoubtedly the expenditure on the hospitals dwarfs all other items. The drug bill, about which so much is heard, has not increased any more since the inception of the service than the other items. At the outset the hospitals received half the total allocation of money for the service. Now they receive 57% as against 9.8% for general practitioner services. The cost of drugs was more than the general practitioners received for prescribing them. In the hospitals the payments to physicians were only 9% of all hospital expenditure and were less than the cost of the patient's food (11% of the total). The estimated total budget for 1958-1959 is $1,907,668,774, of which hospital, specialist, and ancillary services represent $1,223,845,765. In the new budget the hospital services account for more than 60% of the total.

Increased Radioactivity.—The radioactivity over London is measured daily by Kodak Ltd. as part of their control over the manufacture of photographic film. An increase was recently detected, reaching a peak on March 24, when it was 10 to 20 times the normal. After the accident at Windscale, when radioactive iodine escaped into the air, it was 100 times the normal figure. The Atomic Energy Authority confirmed that there has been a small but sharp temporary increase in radioactivity over Great Britain in the second half of March. The increase of radioactivity, which was due to short-lived fission products, is assumed to be the result of recent atomic bomb explosions in Soviet territory.

Duke of Edinburgh President-Elect of British Medical Association.—His Royal Highness Prince Philip, Duke of Edinburgh, accepted the invitation of the British and Canadian Medical Associations to be their president for 1959-1960. Both associations will hold a joint meeting in Edinburgh in July, 1959. This is a return visit of the joint meeting held in Toronto in 1955. This is the first time that a member of the royal family has accepted the position of president of the two associations. Prince Philip became an honorary member of the B. M. A. in 1954. King Edward VII, when Prince of Wales, was made a member in 1900. In 1859, Prince Albert, Queen Victoria's consort, gave the inaugural address as president of the British Medical Association.

Chair of Pediatric Surgery.—Mr. A. W. Wilkinson's appointment to the London University chair of pediatric surgery is the first such appointment in Great Britain. It was established in honor of Lord Nuffield's 80th birthday by the Nuffield Foundation, which has contributed $225,000 for the purpose.

Doctors' Sons not Entering Medicine.—In evidence before the Royal Commission on Doctors' and Dentists' Remuneration, Professor A. M. Claye, said that many physicians are dissuading their sons from entering the profession of medicine because of the lack of financial incentive and added that a different type of person is now taking up medicine as a career. Fewer young physicians now come from the professional classes, and particularly from doctors' homes. This may or may not be a bad thing, but it shows that the professional classes regard medicine as a less satisfactory career than they did formerly. If this is so, it should be viewed with misgiving. The tradition of service and sense of vocation, so essential to the practice of medicine at its highest level, are less readily acquired by those brought up in homes without this background. On the other hand, there is as yet no evidence that the academic standards of the newly

qualified physician are in any way unsatisfactory. The daughters of physicians are not being similarly dissuaded. The reason is mainly a financial one, as the remuneration of the physician is now less than it was before the National Health Service began. Prof. Claye recommended an extension of facilities for private practice, which would be in the interests of physicians, the public, and government funds. At present many patients in ordinary free hospital beds would like the private attention of the physician of their choice, but they are unable to pay for this service owing to the present high charges for a private hospital bed. Private bed accommodations should be provided at a reduced cost.

Area Mortality.—The would-be centenarian should live in London, South-East England, or East Anglia. Statistics published by the Registrar-General suggest that for those wishing to live long Eastbourne would be a good choice. The Registrar-General analyzed deaths between the years 1950 and 1953, which included the 1951 census. This is a change from previous analyses, which covered only the period between censuses. Mortality at all ages combined in the period 1950 to 1953 was higher in the North of England and in Wales than in the rest of England. Of the conurbations, or aggregations of towns, only Greater London had a mortality below the average for England and Wales. Male deaths were greatest in Merseyside. South-East Lancashire had the highest female death rate. The average risk of dying in county boroughs with the highest mortality was 4% greater than in those with the lowest death rates. For males the highest figure in the Metropolitan and county boroughs was at Salford, 27% above the average, and Southwark, 24% above. This is in contrast to the male rate 12% under the average in Ipswich and 8% below at Canterbury, Croydon, and Eastbourne. Female death rates were highest at Oldham and Merthyr Tydfil (23% above average) and lowest in Bournemouth (15% below average) and Westminster (17% below). Salford, Shoreditch, and Southwark showed a male mortality from bronchitis well over twice the average, but at Eastbourne the rate from this cause was more than 60% below average. As regards lung cancer the probability of dying from it is 1.5 times as high in London and the southeast as it is in the north midland region. The *British Medical Journal* of April 12 notes that the value of such analyses is that they draw attention to features in the environment that are damaging to health.

Honor German Surgeon.—The Queen has appointed Prof. Georg Maurer, chief surgeon at the Rechts der Isar Hospital, Munich, to be a Commander of the Order of the British Empire. He is the second German to receive this honor. The surgeon was untiring in his care of the survivors when a British airliner crashed after it had taken off from the Munich airport in a snowstorm. The 23 dead included 8 members of the Manchester United football team. The commendation says: "Nearly all the injured were taken to the Rechts der Isar Hospital, several of them in a critical condition. They received care and treatment of the highest order, and most of the survivors have already left the hospital. All those who have been able to see the work of Prof. Maurer and his staff are agreed that no praise could be too high for the skill and selflessness with which they have looked after their patients. The honor which Her Majesty has conferred on Prof. Maurer is intended to symbolize the appreciation and gratitude not only of the injured but also of the many thousands of British people who have anxiously followed the progress of their recovery."

Contraception.—According to A. S. Parkes (*Family Planning*, 1958, 7, 9), recent work on the hormonal prevention of contraception in man by Pincus and co-workers has depended on the suppression of ovulation and has been made practicable by the preparation of orally active substances with progesterone-like activity. One of these seems to Pincus to be promising. Presumably it overwhelms the follicular phase of the ovulatory cycle partly by local inhibition and partly by interference with pituitary activity. It seems, however, that treatment is necessary over some 20 days in each cycle, probably in order to ensure that ovulation is prevented and not merely postponed, and for this and other reasons this work cannot yet be said to have put oral contraception on a practical basis.

Mammary Cancer.—At a joint meeting of the Liverpool Medical Institution and the Manchester Medical Society on March 6, Dr. Ralston Paterson, director of the Holt Radium Institute, reported that the value of simple x-ray castration was being studied on a series of 750 patients with mammary cancer, and the five-year results for the first 300 showed a real advantage accruing from the use of this procedure. This was more marked the earlier in the course of the disease that the radiation therapy was given. The second study, of the value of prophylactic postoperative irradiation, involved 1,400 patients, and the results from 700 of these after five years were reported. These patients had been divided into those receiving and those not receiving quadrate radiation (primarily flap and axilla radiation) and those receiving and not receiving peripheral radiation (primarily supraclavicular and parasternal radiation). The results were essentially the same whether the patients were treated by irradiation prophylactically or carefully followed up and only irradiated if necessary.

MISCELLANY

"FLAT FILM" OF THE ABDOMEN

Harry L. Arnold Jr., M.D.
and
P. J. Washko, M.D., Honolulu, Hawaii

The time-honored and widely used expression "flat film (or plate) of the abdomen" is an unpopular one among radiologists generally. It deserves to be much more unpopular than it is, however, because there is no general agreement as to what it means.

Its origin is lost in the comparative antiquity of the past half-century. German radiology has no comparable term, and it seems likely that the expression originated in America. Holmes [1] says he recalls its gradually increasing popularity at the Massachusetts General Hospital a few decades ago. The word "plate" referred, of course, to the glass plates used for roentgenograms prior to the introduction of flexible film in 1918. The question is, what was—and is—meant by "flat"?

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Dorland's Medical Dictionary defines "flat" somewhat inadequately as meaning "1. Lying in one plane; having an even surface. 2. Having little or no resonance. 3. Slightly below the normal pitch of sound." The expression "flat film" is not mentioned in this or in any other dictionary consulted.

Webster gives 17 meanings for "flat," of which only three seem relevant: "1. Having an even horizontal surface. . . . 5. Having . . . little thickness. . . . 16. Uniform in hue or shade; monotonous in . . . color. . . ."

Having been told at one time that "flat film of the abdomen" meant an abdominal roentgenogram taken with the patient lying supine (Webster's definition no. 1), one of us was surprised recently by an article [2] in which the first illustration showed a roentgenogram taken with the patient erect, to show air under the diaphragm. The lead sentence of the article referred to the intensive search for means of visualizing concealed organs, beginning soon after x-rays were discovered, which had led to the development of "numerous ingenious techniques, despite which the flat film has remained a major tool in diagnosis." Clearly, to the anonymous author(s) of this article, "flat" meant simply "made without artificial contrast medium"—flat, in other words, in the photographic sense of "lacking in contrast" (Webster's definition 16).

Inquiry among a few roentgenologist friends found them in general agreement that this was not the primary meaning of the term. They thought it meant primarily "taken with the patient lying down, usually supine" (Webster's definition 2). On further inquiry, most agreed that it also ordinarily implied no advance preparation and no contrast medium—but not necessarily so. One of them said it meant, to him, "not stereoscopic" (Webster's definition 5).

Textbooks proved curiously uninformative, considering the wide use of the phrase. Monell, in his book [3] published in 1902, said: "It is certain that one view of a fine stereoscopic x-ray picture is enough to spoil the eye for the usual flat print." No other reference to the word was found. Sussman,[4] writing in 1956, said: "Stereoscopic views are . . . more exact than the single or 'flat' plate." Holmes and Ruggles,[5] writing in 1932, did not use the entire expression anywhere, though they said at one point "so that he may be able to visualize from a flat film the relative depth of objects seen upon it."

In Holmes' eighth edition,[6] however, with Robbins as co-author, this statement occurs: "The roentgenographic examination of the abdomen is founded on the plain or scout film, often termed the flat film or the 'KUB'." On the same page, they add, "On the plain films certain organs can be accurately delineated; others can be seen only in part; and in certain instances only an indefinite suspicion of variation in anatomical structure can be determined."

Frimann-Dahl [7] of Oslo uses "plain film" and "scout film" to designate abdominal roentgenograms made without the use of contrast medium and uses specific expressions to designate the patient's position; nowhere in his textbook did the phrase "flat film" appear. Shanks,[8] in England, refers to "plain radiograms" and "plain films" in which "gas and fluid . . . provide the contrast medium," and he also uses specific expressions to describe the position of the patient. Meschan [9] uses the phrase "plain survey film" or "plain film of the abdomen" to indicate no contrast medium. Sante [10] lends some support to the use of "flat" for this purpose by defining it, in a glossary of terms, as "lack of [since it is an adjective, he meant 'lacking'] contrast between high lights and shadows of a roentgenograph."

The textbooks having failed to agree on this elusive phrase, several prominent American roentgenologists were asked what the phrase meant to them. Most of them said they thought the expression was slangy and ambiguous; one called it "hor-

From the Department of Publications (Dr. Arnold) and the Department of Radiology (Dr. Washko), Straub Clinic.

rible." Some said it was their practice to use in its place such expressions as "scout film" or "plain film." The oldest of the group, Dr. William Newcomet,[11] said he had never known what it meant. Said he:

> As my work in the x-ray field began in 1898, my ideas might be considered just a little "old fashioned" [but] I still try to keep up in a general way. . . . The request for a "flat film of the abdomen" does not seem unusual and I believe it is frequently used. However, when such a request [was made] to me an effort was made, to find out exactly what was expected, and the examination conducted accordingly.

Inquiry was made of 16 other outstanding American radiologists. All replied, and all had more or less definite opinions about the meaning of the phrase. Twelve of them thought it meant just one thing. Five of these thought it meant "taken with the patient horizontal," and three specified "facing the tube." Three of the 12 said it meant "not stereo."

Meanings Assigned to "Flat Film of the Abdomen" by Sixteen Leading American Roentgenologists

Patient's Position	Stereoscopic	Contrast Medium	Alternative or preferred terms
...	...	None	Plain film
Any	...	None	Preliminary film, plain film
Any	...	None	Scout film
Any	...	None	Scout film
Horizontal*	...	None	Plain film, scout film
Horizontal	No	None	
Supine	...	...	KUB film
Recumbent, AP	...	...	Scout film
Supine (facing tube)	...	Yes or no	Preliminary film
Prone or supine	...	...	AP or PA film
Supine	**No**	None	Scout film; KUB film
Supine	Yes or no	Yes or no	
PA or AP	**No**	...	Survey film
...	No	...	Scout film
...	No	...	Exploratory film; scout film
Supine (usual meaning)	**No** (original meaning)	Yes or no	

*Where more than one meaning was given, the meaning stated to be primary or essential is in bold-face type.

Four said it meant "taken without artificial contrast medium." Three of the most forthright and confident replies received [12] were in this latter group.

Three others (seven in all) also voted for "no contrast medium," two decisively and one by saying "some think it also means." One of these three said it also meant "patient horizontal," one said it meant "patient horizontal, and not stereo," and one said it also meant "patient supine, and not stereo." Just one correspondent—who said its original meaning was "not stereo" though it was now often taken to mean "patient supine"—said it did not imply "without contrast medium"! In addition to the three who thought "not stereo" the sole meaning of "flat film," three others included this as a part of their definition of the phrase.

Five thought "horizontal position," variously expressed, was the sole meaning of "flat film," and five others made it a part of their definition. Two said merely "horizontal," one said "PA or AP," and one said "prone or supine;" but four specified "supine" and two specified it indirectly, one by saying "AP" and the other by saying "facing the tube."

Summary

Sixteen outstanding American radiologists were asked to define the term "flat film." The horizontal position received 10 votes, "no contrast medium" 7 votes, and "not stereo" 6 votes, a total of 22 meanings divided among 16 men, of whom 12 chose only one of the three possible meanings, and only two chose all three (see table). It seems clear from this that it would be difficult, if not impossible, to secure general agreement on the meaning of the expression "flat film of the abdomen." It is hopelessly ambiguous and should really be abandoned in casual use as it has been in roentgenologic writings.

Thirteen of the 16 radiologists queried suggested other terms; "scout film" was recommended by 7 and "plain film" by 3. Other terms (see table) were "preliminary film," "KUB," "survey," "exploratory," or "AP or PA." It is suggested that either "scout film" or "plain film" of the abdomen would be generally understood to mean a single (nonstereoscopic) roentgenogram of the abdomen in an unprepared patient and that to either of these phrases should be added a qualifying designation of position: supine (for posterior structures, equivalent to the "KUB"), prone (for the anterior abdomen), upright, or lateral.

Would we had all been as perceptive, and skeptical, as Dr. Newcomet. "Flat film of the abdomen" means, as Frederick O'Brien [13] remarked, "all things to all men." *Requiescat in pace!*

1020 Kapiolani St.

References

1. Holmes, G. W.: Personal communication to the authors.
2. Flat Film of the Abdomen, Pfizer Spectrum **14**:408 (Aug. 15) 1957.
3. Monell, S. H.: System of Instruction in X-ray Methods and Medical Uses of Light, Hot-Air, Vibration and High-Frequency Currents, New York, E. R. Pelton, 1902.
4. Sussman, M. L.: Roentgenologic Diagnosis of Diseases of the Urinary Tract, in Diagnostic Roentgenology, edited by Ross Golden, Baltimore, Williams & Wilkins Company, 1956, p. 588.
5. Holmes, G. W., and Ruggles, H. E.: Roentgen Interpretation: Manual for Students and Practitioners, ed. 4, Philadelphia, Lea & Febiger, 1931.
6. Holmes, G. W., and Robbins, L. L.: Roentgen Interpretation, ed. 8, Philadelphia, Lea & Febiger, 1955.
7. Frimann-Dahl, J.: Roentgen Examinations in Acute Abdominal Diseases, Springfield, Ill., Charles C Thomas, 1951.
8. Textbook of X-ray Diagnosis, ed. 2, edited by S. C. Shanks and P. Kerley, Philadelphia, W. B. Saunders Company, 1950, vol. 3.
9. Meschan, I.: Roentgen Signs in Clinical Diagnosis, Philadelphia, W. B. Saunders Company, 1956.
10. Sante, L.: Manual of Roentgenological Technique, ed. 9, Ann Arbor, Mich., Edwards Bros., 1942.
11. Newcomet, W. S.: Personal communication to the authors.
12. Hodges, F. J.; Schatzki, R.; and Finkelstein, A.: Personal communication to the authors.
13. O'Brien, F. J.: Personal communication to the authors.

THE LEISURE CORNER

LET'S FLY A KITE

Kites were used by Asiatic peoples centuries ago. The Chinese flew kites, and they still do, for fun, at festivals, and to keep evil spirits away from their homes. While the kite is often considered to be a toy, it has many more uses than amusing the flyer on a clear, breezy day. Ancient armies employed kites to hoist men aloft to observe operations behind enemy lines, over hills, or inside forts. Trains of kites have been used in comparatively modern times to lift men. Kites have also been used to carry light cords across river chasms so that a heavier line could then be dragged over and work started on bridges or crossings. A rescue was once effected from an ice floe by dropping a line to the marooned men by means of a kite.

Scientific research has frequently been aided by kites. Almost everyone knows the famous experiment conducted by Benjamin Franklin, who brought electricity out of the sky. In 1749, kites were used by Dr. Alexander Wilson and Thomas Melville, both of Scotland, to carry thermometers into the upper atmosphere, in order to record temperature readings high above the earth. Indeed, weather observations have been made for many years by means of kites carrying small recording instruments. When airplane traffic became too heavy, the United States Weather Bureau found it necessary to stop the use of kites, partly because the wires endangered the planes and partly because more efficient methods of collecting information had been developed.

The world's record for altitude reached by kites was made at a meteorological observation point at Mount Weather, Va., on May 5, 1910, when 10 kites in a train took about eight and a half miles of wire. What a pull that wire must have had! A full crew of men and equipment had to be organized, and the operation took many hours to complete.

With such a long, distinguished history, kites still provide exciting entertainment for both young and old people. The greatest fun lies in building and flying your own kite. Such a project carries one through the stages of planning, construction, and control. In the most rapid succession you find yourself becoming an architect, contractor, and pilot.

The kite and the airplane have a great deal in common. Both stay aloft because of the movement of the air against, across, or around its surface. The airplane has a motor to pull it through and against the air by means of a propeller, thereby making its own breeze. The kite has a cord or arrangement of cords attaching it to its line, and the long string to hold it in position while the wind is pushing against its surface. Both actions hold the heavier-than-air object off the earth, overcoming the force of gravity. The wind moves parallel to the ground and tends to carry the kite along with it. The kite is tilted about a 45-degree angle halfway between the vertical and horizontal and would fly up and away with the wind were it not for the restraint of the line which resists the pull of the wind and holds the kite nearly stationary in relation to the ground.

These two forces fight it out. If the wind wins, the kite rises a little. The angle of the kite's surface increases because of the fixed bridle, affording less resistance to the wind which cannot lift it any higher. The forces have balanced when the wind and the weight and the pull of the kite and line are equal and the kite stays put. The motion of a kite is not always up and down. Kites go sideways, too. They dive, they spin, they weave, they waggle and bob. If kites are to remain steady, the angle of the kite must remain constant. A kite with a plain or flat surface will spin all over the sky unless it has a tail, and no correction from the ground can be effective. The tail acts as a drag in the wind and holds the bottom of the kite toward the earth. All the faults of a kite, especially those of balance and flight, are caused by strong winds. The stronger the wind, the harder the kite is to handle. Therefore, the most desirable time to fly a kite occurs when the breezes are not too strong.

In building a kite it is important to obtain the largest bearing surface and the lightest weight possible. Another principle to remember is never to drive nails or tacks through the stick less they split under pressure. It is important in all symmetrical kites that the opposite surface areas be the same, and all cross sticks evenly balanced. By paying attention to proper balance in weight and surface area, a kite will have the potentialities for increasing the distance it will fly.

Today, the materials used in constructing a kite usually consist of tissue paper in the case of small kites and cloth, and silk or nylon, in the case of larger kites. Cellophane and plastic, easily fastened with tape, are the best of the newer materials. Since the wood sticks of a kite must be able to withstand the pressure of the wind against the cover, pine and cypress are very good woods to use, for the grain is usually straight, and the material is light and of moderately good strength.

Many fishermen find a kite useful when they want to fish off shore and have no boat. After the kite is launched, they attach the fish line to the main kite line with a ring or a loop of thread; the fish line will be carried out over the water, and then the bait is dropped. When the fish strikes, a good jerk breaks the loop and the fisherman reels in his fish. A large kite can pull a small wagon on a smooth road, and a smaller kite is able to drag a sled on smooth ice. If you can float on your back, you can do as Benjamin Franklin did, let a kite take you across a pond or small lake. There are many novel uses for kites. This will depend on your ingenuity. You can create your own fun as you become adept in building and flying them. And if your kite winds up in a tree, just think of the fun you have had in seeing it reach that height.

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MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Observations on Carotenemia. The Lord Cohen of Birkenhead. Ann. Int. Med. **48**:219-227 (Feb.) 1958 [Lancaster, Pa.].

Yellowish pigmentation of the skin (xanthodermia) is most frequently due to jaundice, but it may also be caused by the ingestion of substances, such as picric acid, saffron, or Atabrine, or by the excessive intake of carrots or other foods containing carotenoids. If it is due to this last cause, it is usually referred to as carotenemia, but it has been described also under such terms as aurantiasis and carotenosis cutis. Carotenoids occur in all green vegetables and especially in carrots; they are also found in butter, eggs, and oranges. Their general formula is $C_{40}H_{56}O_6$; the hydrocarbons are termed carotenes, and the hydroxyl derivatives xanthophylls. Beta-carotene is the most important precursor of vitamin A. Normally, 100 ml. of blood contains 100 mcg. of carotenoid, and the ratio of xanthophyll to carotene is 2:1.

Carotenemia may be brought on by various causes. First, there is the excessive intake of carrots. The author observed 50 cases of this type in Britain, mostly during the war when people were urged to eat carrots by the Ministry of Food. In recent years a raw carrot diet to induce slimming has been a cause. Persons have been known to eat from 4 to 8 lb. of carrots daily. In these xanthodermia tended to appear after 6 to 8 months; if carrots were then omitted from the diet, the yellowish tinge faded in 2 to 6 weeks. The main sites of the pigmentation were the face (especially the nasolabial folds) and the palms and the soles. The mucous membranes and the conjunctivas were clear, and no carotene was found in the urine.

Excessive carotene in the blood can be demonstrated and distinguished from jaundice by the simple method of Greene and Blackford: Equal volumes of serum, absolute alcohol, and petroleum ether are shaken together in a test tube and left to stand. In carotenemia, the top layer of petroleum ether shows a yellowish discoloration. In jaundice, it is in the middle layer of alcohol that the bile pigments are dissolved, and these often color also the bottom layer of precipitated proteins. Carotene often rose to 500 mcg. per 100 ml. of blood in this group of cases.

Carotenemia is observed also in patients with diabetes mellitus. It is believed that 2 factors are active in these cases: excessive intake and hyperlipemia. Other hyperlipemic states, such as nephrotic syndromes, hypercholesteremic lipoidoses, and hypothyroidism, have been known to be accompanied by hypercarotenemia. In this connection the author comments on carotenemia in patients with myxedema and on carotene and thyroid function. An inborn error in metabolism, in which there exists a defective conversion of carotene into vitamin A, is mentioned as another cause of carotenemia. The history of a woman is cited to illustrate this condition. The evidence that this patient's hypercarotenemia was due to failure of conversion of carotene into vitamin A is summarized as follows: (1) absence of excess of carotene from the diet; (2) persistent hypercarotenemia with low carotene intake over several years; (3) normal blood lipids; (4) vitamin A deficiency, although absorption of vitamin A was normal; and (5) carotene content of the serum constantly greater than its xanthophyll content. What appeared to be primarily a hypercarotenemia was accompanied by a moderate degree of hypothyroidism.

Thesaurosis Following Inhalation of Hair Spray: A Clinical and Experimental Study. M. Bergmann, I. J. Flance and H. T. Blumenthal. New England J. Med. **258**:471-476 (March 6) 1958 [Boston].

The authors report on 2 women, aged 27 and 22 years, respectively, who had had previous roentgenologic examinations of the chest with completely normal findings. Both patients were free of respiratory signs or symptoms, but in both a routine x-ray examination of the chest revealed diffuse bilateral pulmonary infiltrates and hilar lymphadenopathy. This roentgenographic appearance of the chest suggested that inhalation of a noxious agent might be the cause of the lesions. To anyone who has seen hair-spray users envelop themselves in great clouds of mist, often spraying the hair above the forehead in such a manner that the spray is directed straight at the nose and mouth, there can be no question that considerable inhalation

The place of publication of the periodicals appears in brackets preceding each abstract.

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might occur in some cases. Both patients had had the habit of spraying their hair twice daily for about 2 and 3 years respectively. Microscopic examination of tissue could be carried out in the case of only 1 patient, from whom a scalene lymph node was excised. The lesion found, although superficially resembling sarcoidosis, was distinctly different from it on histological grounds, showing a foreign-body granuloma typical of those produced by the parenteral introduction of macromolecular substances.

The only fractions of hair spray that need to be seriously considered as capable of granuloma formation are the resinous substances and lanolin. Lanolin could conceivably give rise to a lipid pneumonia, but the histological appearance of such a process would have differed from that found in the patient. Hair spray of a well-known brand was allowed to evaporate to dryness. The residue was suspended in sterile isotonic sodium chloride solution, and varying amounts of this suspension were then injected subcutaneously into the inguinal regions of 3 guinea pigs. The injected hair-spray residue acted like a typical macromolecular substance. It brought about a granulomatous inflammation at the site of the injection, and it was detected in the reticuloendothelial cells of the liver and spleen. An inflammatory reaction, which was probably due to the presence of the material in reticuloendothelial cells, was also found in the lungs of 2 guinea pigs kept for 75 days. These findings lend weight to the authors' view that in all likelihood the lesions in the lymph nodes and lungs of the 2 patients were due to the inhalation of macromolecular substances contained in hair spray. In both patients the roentgenographically visible lesions disappeared about 3 months after discontinuation of the use of hair spray.

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The Etiology of Common Respiratory Infections in a Civilian Adult Population. H. G. Grieble, G. G. Jackson, H. F. Dowling and others. Am. J. M. Sc. **235:**245-260 (March) 1958 [Philadelphia].

Acute respiratory infections were studied in 62 men and 60 women, between the ages of 18 and 56 years, working in clerical, technical, or professional positions in a large city. The disease was ascribed to influenza viruses in 10 patients, beta-hemolytic streptococci in 7, and adenoviruses in 4. The disease was serologically compatible with infectious mononucleosis in 2 patients, and a clinical diagnosis of Coxsackie virus infection was made in 6 patients. Thus, the acute respiratory infections were caused by unknown or undetected agents in 93 patients (75%), by known viruses or presumably caused by viruses in 22 (19%), and by hemolytic streptococci in 7 (6%). Twenty-nine of the 122 patients had fever. Sixty-three (52%) of the patients had afebrile illnesses, the causation of which was unknown and the predominant symptom of which was acute coryza or sore throat. In 27 patients (22%) the acute respiratory disease was characterized by pharyngitis with fever, pharyngeal exudate, or conjunctivitis.

These data show that among civilians the nonepidemic occurrence of febrile acute respiratory disease, pharyngoconjunctivitis, and nonbacterial exudative pharyngitis was infrequently caused by adenoviruses. The authors' findings thus suggest that immunization with adenovirus vaccine would not substantially reduce acute respiratory diseases in a civilian population. Influenza viruses, types A, B, or C, caused 25% of the febrile illnesses. Bacterial species other than hemolytic streptococci that are considered potentially pathogenic for man were most common among patients with febrile acute respiratory disease and conjunctivitis, but their causative importance was considered doubtful. The differentiation of common respiratory infections into distinct clinical syndromes has valuable diagnostic and therapeutic implications. The clinical identification of streptococcic pharyngitis was made in 60% of bacterial infections, while that of specific agents was made in only 20% of viral infections. The latter was little better than chance.

SURGERY

Results of Operations on Patients with Fibrous Dysplasia of Bone. K. Chiari. Wien. med. Wchnschr. **108:**149-151 (Feb. 15) 1958 (In German) [Vienna].

The author reports on 4 female patients with fibrous dysplasia of bone, who were operated on at the ages of 41, 17, 10, and 8 years, respectively, at the first surgical clinic of the University of Vienna. The typical findings in this disease are cystic transparencies in the bones; these are unilateral in most patients. The onset of the disease takes place in early childhood; the disease progresses during infancy and usually remains stationary at the time of puberty. The bones are somewhat sclerosed in the areas adjacent to the cysts. The anatomicopathological examination reveals that the transparencies visible in the roentgenogram are pseudocysts filled with fibrous tissue.

The 41-year-old patient was operated on after her condition had remained stationary, and firm bony repair was obtained with the aid of a subtrochanteric and supracondylar osteotomy of the femur. There was delayed callus formation which, however, was not considered abnormal since the sclerosed bone appeared to be very thin subtrochanterically at the site of the osteotomy and the fibrous dysplasia may not have been responsible for this finding. The 17-year-old patient was operated on twice. At the first operation at the age of 10 years, when her disease was still progressive, the patient showed precocious puberty, and roentgenologic examination revealed coxa vara of 80

degrees for which a subtrochanteric osteotomy was performed; a cyst was not demonstrated roentgenologically in the area of the osteotomy, and bone repair was normal. Seven years later the patient had a minor accident, in which a fracture of the femur occurred, for which she was treated elsewhere by a plaster cast. Bone repair was unsatisfactory, and repeated roentgenograms showed involvement of the entire left half of the skeleton by cysts. Repeated osteotomy of the fractured bone resulted in a completely normal bone repair.

The 2 other patients were operated on directly in the cystic area. The 10-year-old patient, with severe deformity of the right lower extremity, pronounced asymmetry of the cranium, scoliosis, precocious puberty, and conspicuous pigmented nevi of the skin, was treated by osteotomy of the right femur; apparently strong callus formation resulted in clinical firmness and stability, while the roentgenogram showed a high degree of atrophy and disintegration of the bone in the area of the osteotomy. In the 8-year-old patient, with a monostatic form of fibrous dysplasia of the left femur, the osteotomy was followed by pseudarthrosis, and reoperation revealed transformation of the entire trochanter region into a soft spongy bone mass. This, however, was able to assume a normal form and almost normal structure as a result of fixation of the limb in a plaster cast for 1 year and immobilization for 6 months, after which walking exercises were started.

As a rule, surgical correction should be performed as rarely as possible in the progressive stage of fibrous dysplasia of bone, and the operation, when necessary, should be performed in an area of the bone which is roentgenologically healthy and in which normal growth of bone and bone repair may be expected. To prevent deformities, prophylactic support of the lower extremity by removal of load is indispensable. It could be assumed that a small rupture of a cyst would exert an effect similar to surgical intervention in the area of the cyst and would, therefore, cause an exacerbation of the disease. It was possible to carry out simple correction of position in all patients in the inactive stage of the disease, after the condition became stationary, and the callus formation was considered to be normal.

Imperforate Anus. E. J. Donovan and E. G. Stanley-Brown. Ann. Surg. **147**:203-213 (Feb.) 1958 [Philadelphia].

The authors review observations on 21 infants and children with imperforate anus, who were observed over the 10-year period from 1946 to 1956, and all except 1 of whom were cared for by the authors. They describe the embryology and anatomy of imperforate anus and differentiate 4 types of this deformity. Type 1 is a stenosis of the anus or lower rectum, which is actually an incomplete or partial perforation; type 2 consists of a persistant thin anal membrane; type 3 is the most common form reported, and in this deformity the rectum terminates as a blind pouch ending at a variable distance from the perineal skin; in type 4, the rarest variety, both the anal canal and the lower rectum end as blind pouches which do not communicate and the distance between the 2 structures is variable. More than one-half of the patients in this report were girls with type 3 imperforate anus with associated rectovaginal fistula. The term "posterior vaginal anus" describes this most common form seen in female infants and children. The anal opening in these patients looks much like a normal anal orifice except that it is in the posterior part of the vaginal wall and is surrounded by mucous membrane instead of skin.

There were 9 male and 12 female patients; 4 died, and 2 were not operated on. Three had type 1, 2 had type 2, and 1 had type 4 imperforate anus. Of the 15 patients with type 3 imperforate anus, 11 were girls with associated rectovaginal fistula or, as the authors prefer to call it, posterior vaginal anus. In this form a perineal operation is undertaken, preferably at 4 or 5 months and certainly before the menarche. In a newborn infant, surgery should be delayed for at least 48 hours to allow time for recognition of associated congenital defects. The external anal sphincter develops independently, arising from regional mesoderm at the site of the anal dimple, and has no relation to the hind gut. It is essential to determine the exact location of the external anal sphincter in order to perform a satisfactory anoplasty. Excision of the coccyx is never indicated.

In older children with posterior vaginal anus, a secondary megacolon often develops. This should be decompressed with a proximal colostomy before initiating definitive correction of the congenital anal defect. A completely divided transverse colostomy located in the right upper quadrant functions best and leads to the fewest complications. The authors prefer the Devine type of double-barreled colostomy with complete separation of the stomas by a bridge of fascia and skin. Thorough cleansing of the intestine is essential. The surface wetting agents proved helpful in maintaining soft stools both before and after surgery. It is particularly important to cleanse adequately the distal loop of a colostomy, prior to any surgical procedure. When malnutrition accompanies imperforate anus, weight gain and improvement in general health will follow the construction of a colostomy. X-ray examination of the colon with Lipiodol, never barium, is apt to be misleading, both in regard to the presence or the absence of secondary megacolon and in the determination of distance between the anal dimple and the posterior vaginal anus. Where the opening of a posterior vaginal anus is located high up, near

the cervix, a combined abdominoperineal approach is indicated. Postoperative dilatation of the new anus is a vitally important part of the treatment and must be continued by the mother. Persistent bowel training is essential.

Management of Pain Due to Pelvic Malignancy: A Follow-Up of 122 Cases. M. D. Simionescu. Zentralbl. Neurochir. 17:284-288 (No. 5) 1957 (In English) [Leipzig, Germany].

The author reports observations on 122 patients with intractable pain due to pelvic malignancy, who were treated between 1935 and 1956 at the Neurosurgical Clinic of Bucharest. The following factors may give rise to painful stimuli: (1) mechanical pressure exerted by the tumor on the pain receptors; (2) local ischemia due to arterial occlusion; (3) marked venous stasis in the pelvic viscera; (4) increased production of acid metabolites and potassium as the result of local hyperemia and tissue destructions; (5) involvement of the small arteries and their sympathetic plexuses; and (6) continuous irritation of the nervous plexuses of the pelvis by the invading tumor. Some of these factors cause disturbances in the physiology of pain receptors, lowering their threshold of excitation. In this way, even subliminal stimuli, usually painless, may elicite pain.

Anterolateral chordotomy was performed in 62 of the patients; in 22 of them the chordotomy was bilateral (carried out in 2 stages). In some patients the complications of chordotomy were considerable. Twenty-two patients experienced a slight paresis either in the ipsilateral leg or in both legs, which disappeared after 3 to 6 weeks (9 patients were already bedridden). Fourteen patients with unilateral and all with bilateral chordotomy complained for 3 to 6 weeks of impaired anal and bladder function, but in none were the sphincters permanently impaired. The results as regards relief from pain were satisfactory. Forty-one of the patients were still free from pain 12 months later. Five others were free from pain at the time they left the hospital, but no follow-up was possible. In 16 patients, the pain recurred 5 to 6 weeks later, either in the same side (10 cases) or in the opposite side (5 cases), but 14 of these responsed to intrathecal alcohol injection.

The intrathecal alcoholization of the posterior spinal nerve roots was also employed in the remaining 60 of the 122 patients who had been subjected to chordotomy. The procedure is as follows: One hour previous to the alcohol injection the patient is given a basic analgesic. Then 3 spinal puncture needles are successively inserted into the subarachnoid space between the spinal processes of the vertebrae L-3, L-4, L-5, and S-1. After checking the position of the needles, 0.5 to 1 cc. of alcohol is injected under slight pressure through each needle. The injection is instantly followed by a sensation of warmth or burning, giving place a few seconds later to a slight hypoesthesia in the cutaneous areas of the alcoholized posterior nerve roots and followed after 10 to 15 minutes by a complete analgesia. The intrathecal alcoholization is especially indicated in patients in a poor state of health, as well as in those who have become drug addicts and who could not stand the risks of a chordotomy, also in those who do not accept the operation. This method proved to be useful in patients with pain restricted to a few nerve roots and in patients complaining of residual pain after a chordotomy.

Late Results of Transplantation of the Tibial Tubercle in Recurrent Dislocation of the Patella. T. Jerre and B. Knutsson. Acta. orthop. scandinav. 27:141-152 (No. 2) 1957 (In English) [Copenhagen].

The authors accept Blumensaat's classification of dislocations of the patella, which differentiates the following groups: (1) recent dislocations; (2) recurrent dislocations, that is, dislocations occurring at intervals with the patella in proper position in the meantime; (3) constant dislocations. These are subdivided as follows: (*a*) habitual dislocations that occur every time the knee joint is flexed and (*b*) permanent dislocations in which the patella is always in a dislocated position. The paper is concerned only with those types of dislocations belonging to the Blumensaat group 2. Several surgical methods have been described for this form of recurrent patellar dislocation, but at the department of orthopedics in Hälsingborg transplantation of the tibial tubercle has been used during the last 20 years. This operation, which was recommended as early as 1888 by Lauenstein, is performed by the authors in the following way: A lateral lambdoid incision is made over the knee joint and extended a short distance proximal to the base of the patella and a few centimeters distal to the tibial tubercle. The ligamentum patellae is dissected, and the tibial tubercle is chiseled off. The ligamentous capsule of the knee on the outer side is slit longitudinally up to the level of the base of the patella. A thin bone flap is then chiseled up medially below the original site of the tibial tuberosity, and the tibial tuberosity is fixed under this bone flap, usually with a Rissler pin and a few absorbable (catgut) sutures, about 1 cm. medially and 1 cm. distally to its original site. After suturing the subcutaneous tissue and skin, the knee joint is fixed in a plaster cast with the knee flexed at about 10 degrees. The plaster is removed after 6 weeks, after which active and passive movements are begun.

This operation was performed on 32 joints in 28 patients, whose ages ranged from 15 to 45 years. There were no primary surgical complications. All

28 patients could be traced at the time of follow-up, from 1.1 to 19.7 years after operation. All except 1 patient, who was living abroad, could be reexamined. Eighteen patients stated that they had been free from symptoms since operation; 4 had had recurrences in the form of dislocations or subluxations. The region over the tibial tubercle was tender to palpation in 8 patients. In no instance was this sign severe, and on inquiry all 8 patients stated that this region only gave them a little trouble when they were kneeling on something hard. About one-third of the knee joints operated on showed a somewhat decreased range of flexion. Extension was not impaired in any. In general, symptoms were few and slight, but roentgenologic examination revealed arthrosis deformans in the knee joints of most of these patients. It is suggested that these changes might progress with time and might later cause symptoms in patients who are now free from them.

Technique and Results of Isolation of Cancer Cells from the Circulating Blood. S. Roberts, A. Watne, R. McGrath and others. A. M. A. Arch. Surg. **76:** 334-346 (March) 1958 [Chicago].

A physiological method for the isolation of cancer cells from blood utilizing differences in specific gravities is described. Step 1 of the procedure is the elimination of erythrocytes from whole blood, and step 2 is the separation of cancer cells from leukocytes. The erythrocytes are eliminated by the addition of fibrinogen, which causes rouleaux formation of erythrocytes and hence their accelerated sedimentation. The leukocytes and the tumor cells remain in the supernatant plasma in a homogenous suspension. This plasma suspension then is decanted and layered, maintaining a sharp interface, over 5 cc. of isosmotic albumin solution which has been adjusted to a specific gravity of 1.065; this specific gravity is intermediate between that of most adenocarcinoma cells and leukocytes. After centrifugation most of the leukocytes, which are heavier than the adjusted albumin, will be packed in the bottom of the centrifuge tube, while most of the tumor cells, which are lighter than the adjusted albumin, will be collected at the plasma-albumin interface. The tumor cells are then aspirated from the albumin-plasma interface, resuspended in 10 cc. of isotonic sodium chloride solution, and centrifuged. This resuspension of the cells and recentrifugation remove albumin, which causes an undesirable red precipitate with the Papanicolaou stain. In order to improve the accuracy of differentiation of tumor cells and normal blood cells, the cancer cells isolated by this technique are compared with a direct smear of the tumor.

A total of 100 patients, 41 of whom had cancer of the digestive tract, 25 had cancer of the breast, 14 had cancer of the genitourinary tract, and 20 had miscellaneous cancers, and 14 control patients with nonmalignant diseases were studied by this technique. Blood samples were obtained from 1 or all of 3 venous sources: (1) peripheral blood samples from antecubital venipuncture; (2) aspiration of blood from a catheter inserted into the major venous trunk draining the tumor area; and (3) direct needle aspiration of blood from a vein draining the tumor site. Cancer cells were detected in the circulating blood from any or all of the 3 venous sources in 17% of patients who had been classified as curable and in 31% of those classified as incurable, indicating a direct relationship between the advancing stage of the malignant disease and the percentage of positive blood samples. Of 7 patients operated on, for whom adequate data before and during the surgical intervention were available for the evaluation of the role of the surgical manipulation, 6 showed an increase in the number of cancer cells in the circulating blood during manipulation incident to resection of the tumor. In 2 carefully studied patients, the cancer cells disappeared from the circulating blood within minutes after the removal of the primary carcinoma.

NEUROLOGY & PSYCHIATRY

Influence of Prior Active Immunization on the Presence of Poliomyelitis Virus in the Pharynx and Stools of Family Contacts of Patients with Paralytic Poliomyelitis. P. W. Wehrle, R. Reichert, O. Carbonaro and B. Portnoy. Pediatrics **21:**353-361 (March) 1958 [Springfield, Ill.].

Sixty-seven persons, 12 being patients with paralytic poliomyelitis and 55 being family contacts of these patients, were studied by the authors in an attempt to obtain information regarding the degree of resistance to inapparent infection which may be conferred by immunization with formalized poliomyelitis vaccine, and to determine the influence of previous immunization on the quantity of poliomyelitis virus which can be detected in the pharynx and the feces. Isolation of poliomyelitis virus from the feces and from pharyngeal secretions of the immunized and nonimmunized household contacts of the patients with paralytic poliomyelitis showed that previous immunization does not prevent the acquisition of inapparent infection with poliomyelitis virus under conditions of household exposure. Although there was no apparent interference with enteric multiplication of poliomyelitis virus, an accurate estimate of the relative rates of acquisition of infection with poliomyelitis virus between immunized and nonimmunized children of comparable ages was not possible. However, enteric infection with poliomyelitis virus

appeared to be slightly less frequently observed among the children household contacts in the age group from 5 to 9 years, toward which the immunization programs have been directed during the past 2 years, so that the members of this group were most frequently immunized. Poliomyelitis virus was present in the pharyngeal secretions of previously immunized contacts of patients with paralytic poliomyelitis less frequently and in lower titer during the study period than in those who had not previously received poliomyelitis vaccine.

Pharyngeal virus appears to be more sensitive to the presence of antibody than is enteric virus, and antibody is present in the pharyngeal secretions relatively early in the course of poliomyelitis infections. Thus, virus in this area might reasonably be expected to be neutralized more rapidly if the antibody-forming mechanisms were sensitized by previous immunization. Although there is no evidence that the air-borne route is important in the transmission of poliomyelitis, it seems reasonable to suspect that, in areas of good environmental sanitation and high standards of personal hygiene, contact transmission of pharyngeal virus may be important in maintaining this agent in the human population, particularly in view of the relatively high titers of virus observed in the pharynx. The authors' findings would suggest that this route may be rendered less effective after immunization.

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An Analysis of Residual Disabilities (Paralysis and Crippling) Among 100,000 Poliomyelitis Patients: With Special Reference to the Rehabilitation of Postpoliomyelitis Patients. K. S. Landauer and G. Stickle. Arch. Phys. Med. **39:**145-151 (March) 1958 [Chicago].

More than 300,000 persons alive today in the United States have had paralytic poliomyelitis, and more than 50% of them were attacked in the last decade. An estimated 90% of these recent poliomyelitis patients were reported by their physicians as severely, moderately, or slightly crippled at last notification. Of 102,184 patients hospitalized for poliomyelitis in the United States between 1952 and 1956, the cases of 64,146 with paralytic poliomyelitis were analyzed for residual disability or crippling in terms of the anatomic site or sites (most frequently multiple) affected. In addition, the records of 42,983 patients, aged 3 years and over, were analyzed for functional disabilities or, conversely, for remaining self-care capacity.

Of the 64,146 patients, 983 (1.5%) were totally paralyzed, 1,605 (2.5%) had severe paralysis of both arms and both legs, 3,749 (5.8%) had severe paralysis of both arms, and 9,900 (15.6%) had severe paralysis of both legs; 10,233 (16%) had some paralysis of 1 arm, 14,662 (22.9%) had some paralysis of both arms, 18,578 (29%) had some paralysis of 1 leg, 29,067 (45.3%) had some paralysis of both legs, and 9,600 (15%) had some degree of respiratory paralysis. At the time of discharge from the hospital, no residual disability (paralysis) was found in 10.2% of the 64,146 patients; there was slight disability in 22.4%, moderate disability in 41.1%, and severe disability in 26.3%. Functional disability at the time of discharge from the hospital was recorded as follows in the 42,983 patients: 13.6% were confined to bed, 6.7% were able to use the wheel chair only, 3.5% were able to stand only, 33% were able to walk with aids, and 43.2% were able to walk unaided. Self-care capacities among these 42,983 patients were recorded as follows: 24.4% of those confined to bed, 32.9% of those able to use the wheel chair only, 62.7% of those able to stand only, 81.7% of those able to walk with aids, and 92.6% of those able to walk unaided, were able still to feed, dress, and toilet themselves. Experience in 16 respiratory and rehabilitation centers shows that today's "hopeless" patients need not remain helpless, for through such integrated programs of research, care, teaching, and training comes the promise of help for even the most severely disabled.

Left Cerebral Hemispherectomy for Glioma in Infant Five Months Old. R. Cordero and F. Lichtenberg. Bol. Asoc. méd. Puerto Rico. **50:**18-29 (Jan.) 1958 (In Spanish) [Santurce].

An infant, 5 months old, was hospitalized for the treatment of diarrhea and vomiting which had lasted 5 days. There was no fever. Moderate hydrocephalus and enlargement of the anterior fontanelle were observed. There were no neurological symptoms. Inasmuch as a subdural effusion or a chronic hematoma was suspected, repeated subdural puncture and examination of the cytochemical constituents of the spinal fluid were made. The quantity of fluid in the left subdural space was greater than in the right. After a few days of hospitalization and treatment, the digestive disorders disappeared. Hydrocephalus and enlargement of the anterior fontanelle, however, remained unchanged. Given a diagnosis of a subdural effusion or a chronic hematoma, the patient underwent a surgical exploration of the left hemicranial cavity 6 weeks after hospitalization. A cystic-nodular tumor which occupied almost all the left cerebral hemisphere was discovered and was removed by a left hemispherectomy. The patient stood the operation well; at the end, however, he stopped breathing and was pulseless for 20 minutes. He recuperated upon administration of oxygen, blood transfusion, intramuscular administration of neosynephrine, and the like. The tumor was pathologically classified as astrocytoma, grade 3. Samples of the tumor were sent to other pathologists. It was commented upon "as a most interesting combination of connective and glial tissue. One could hardly call it a neo-

plasm; it must be some sort of heterotopia of the nervous tissue. Tissue of this combination has been observed in superficial lesions of the cerebellum where the neuroepithelial tissue has not differentiated itself very well from the leptomeninx." The tumor has been provisionally designated as choristoglioma.

At the time of writing the patient is 18 months old. His head is slightly rotated to the left. He has facial paralysis on the right-central side, nystagmus with certain ocular movements, normal pupils, and right-sided spastic paralysis with conservation of voluntary movements of the legs. The Rossolimo sign is present in the right foot and moderately present in the left foot. Up to this age, the child has not spoken. The electroencephalographic records of the empty hemicranium show some electric activity. These records show a progressive tendency to normal stabilization. They also show asymmetrical waves of smaller voltage in the left side than in the right and epileptogenic tracings in the right side.

GYNECOLOGY & OBSTETRICS

Leukemia from Gynecologic Viewpoint. B. Fjällbrant. Nord. med. **59**:177-179 (Jan. 30) 1958 (In Swedish) [Stockholm].

During the last 10 years 11 patients with leukemia were treated in the obstetric and gynecologic department in Lund and Malmö and the radiotherapy department in Malmö. From the gynecologic viewpoint leukemia is of greater importance than was formerly supposed. There are leukemoid infiltrations and ulcerations in the genital organs, and leukemia may cause menstrual disorders and abdominal pain. Only 1 patient was pregnant. Pregnancy rarely occurs in leukemia. No case of transmission of leukemia to the infant has been reported. Most authors believe that pregnancy does not shorten the time of survival in acute or chronic leukemia.

Statistical Contribution to Problem of Etiology of Carcinoma of the Uterine Cervix: Its Incidence in Relation to Number of Births. K.-W. Franke and A. Eydam. Ztschr. Geburtsh. u. Gynäk. **149**:297-323 (No. 3) 1958 (In German) [Stuttgart, Germany].

Whereas in some countries the death rate from cancer is now higher among men than among women, deaths from cancer in Germany were still more frequent among women than among men as late as 1950, the ratio being 42 to 36. This excess of cancer deaths in women is largely due to the frequency of carcinoma of the uterine cervix, which has remained high despite the efforts at cancer prophylaxis. The authors believe that a number of factors play a part in its development. Frequent deliveries and abortions have long been suspected as a contributing factor, and more recently endocrine factors have been suggested. The authors made statistical studies on the incidence of cervical carcinoma in relationship to the number of births at the women's clinic of the University of Erlangen, where 6,090 patients with cervical carcinoma were compared with 10,000 women with gynecologic disorders who were free from tumors. The average number of births for the patients with cervical carcinoma was 4.24, whereas for the control group of women it was 2.5. The authors, like other investigators, found that cervical carcinoma is most frequent in women between the ages of 45 and 55 years and that after the menopause the incidence of cervical carcinoma decreases noticeably. Patients with cervical carcinoma had a higher than average fertility. Carcinoma of the uterine cervix was considerably more frequent in women who had had several children than in women who were never pregnant. The authors conclude that, on the basis of their own observations and those of other investigators, the follicular hormone apparently plays a certain part in the pathogenesis of carcinoma of the uterine cervix, although other factors may appear to be even more important.

The Hazards of Elective Induction of Labor. W. C. Keettel, J. H. Randall and M. M. Donnelly. Am. J. Obst. & Gynec. **75**:496-510 (March) 1958 [St. Louis].

The staff of the department of obstetrics and gynecology of the State University of Iowa Hospitals has had an extensive experience with the elective induction of labor at term. Obstetric patients come from all parts of the state, and when pregnancy is uncomplicated, they are brought to the hospital 2 weeks before term. The hospital facilities for such antepartum patients are limited. Because of the serious overcrowding, labor was induced in many of the indigent patients. Between 1926 and 1956, there were 28,253 patients delivered; labor was electively induced at term in 6,860 (24.3%) of this number. None of these patients had medical complications requiring induction, and all infants were alive and judged to be of term size at the time of induction. Each chart was reviewed, and the pertinent data placed on a standard punch card for ease of analysis.

Summarizing the results of this analysis of 6,860 electively induced labors, the authors state that the most effective method of inducing labor is simple amniotomy. Eighty-two and three-tenths per cent of the patients were in labor within 4 hours, and only 2.3% had a latent period of over 24 hours. Pitocin stimulation was used in patients with prolonged latent periods or desultory labors with intrapartum fever. Cesarean section must be considered when the latent period is prolonged and infection is present, if labor cannot be stimulated

within 24 to 36 hours. There was 1 maternal death related to induction. The principal fetal hazards were prematurity, 3.1%; prolonged latent period, 5%; malpresentation, 0.9%; and prolapse of the cord, 0.3%. There were 6,889 babies born. Of these, 37 (or 0.6%) were stillborn, and 55 (or 0.8%) died during the neonatal period. The perinatal mortality was 1.4%. Thirty-nine of the perinatal deaths (0.6% of the babies delivered) were directly related to the elective induction. A conservative attitude should be maintained by the specialist toward the elective induction of labor. The average general physician should allow labor to start spontaneously.

Labor After Mitral Commissurotomy. G. Dellepiane. Minerva med. **49**:1-3 (Jan. 6) 1958 (In Italian) [Turin, Italy].

Twenty-three women underwent mitral commissurotomy, 20 of them during pregnancy and 3 a few years (on an average 3 years) before pregnancy. Mitral commissurotomy was performed during the 3rd month of gestation in 7 patients, during the 4th month in 10, during the 5th month in 2, and during the 6th month in 1. Almost all the patients had a pleural reaction after the operation, in some instances accompanied by mild effusion, which subsided shortly. The uneventful postoperative course and freedom from recurrence of the rheumatic process were probably due to the protection afforded by cortisone which was related to gestation. From the obstetric point of view, labor was normal in 21 women. Two women had postoperative abortion. Anoxia related to the cardiovascular decompensation caused the intrauterine death of the fetus in 1 primipara during the third month of gestation. Circulatory decompensation in this patient had been corrected by the mitral commissurotomy. The abortion in the other, a multipara occurred during the 6th month of gestation and was probably unrelated to a cardiac disorder. This patient underwent the operation 3 years before pregnancy. Fourteen women had delivered up to the time of the writing of this report, while the others were still pregnant. The onset of delivery was spontaneous in all women. The delivery was carried out normally in 7, by the aid of forceps in 6, and by cesarean section due to obstetric condition in 1. Hemodynamic disequilibriums were not observed in any instance. Acute pulmonary edema developed in 1 woman at the beginning of the postpartum period. It was probably due to the failure of the previous surgical procedure to correct completely the mitral stenosis. Four women (30%) were allowed to breast-feed their infants.

The author recommends that women in whom mitral stenosis is discovered during pregnancy should have the operation performed during pregnancy unless it is specifically contraindicated. This opinion is based on 2 facts: 1. There is a mortality of 7 to 10% during the puerperium in women in whom mitral stenosis has not been corrected by commissurotomy. 2. There have been no postoperative complications attributable to mitral commissurotomy.

Caesarean Section at the Winnipeg General Hospital Maternity Pavilion, 1951-1956. C. R. Bradford. Canad. M. A. J. **78**:392-397 (March 15) 1958 [Toronto].

The data presented here were taken from the records of the maternity pavilion of the Winnipeg General Hospital from Jan. 1, 1951, to Jan. 1, 1956. Procedures included as cesarean sections were those performed on a patient from the 28th week of pregnancy onward or those in which the fetus weighed more than 500 Gm. (1¼ lb.). There was a total of 19,379 deliveries. Of this number, 476 were by cesarean section. This is an incidence of 2.45%. In 1951 the incidence was 2%, and since that time there has been a gradual increase to 2.8% in 1955. There were no maternal deaths due to, or associated with, cesarean sections. During the same period of time there were 7 maternal deaths among 18,903 vaginal deliveries, an incidence of 3.7 per 10,000. On examination of the records of the 7 patients, it was found that in no case would a cesarean section have influenced the final outcome.

The use of the classical method of cesarean section has been decreasing in most obstetric hospitals, and this has also been the case in Winnipeg. However, of the 476 sections studied, 85 (or 18%) were of the classical type. This rate is regarded as too high, but 62 of these were done by physicians and surgeons who did not limit their practice to obstetrics and gynecology. The indications for cesarean section accepted at the Winnipeg hospital are those formulated by Bryant in 1950, the major ones being (1) mechanical obstruction to delivery, (2) bleeding, and (3) hypertensive disease. There were 295 primary cesarean sections, 177 repeat sections, and 4 sections after previous hysterotomy. For primary sections, more than 1 indication was often given. Sections in which there were obstetric or medical complications that would probably influence the immediate outcome for mother or baby were considered as emergency procedures. There were 174 emergency and 302 elective sections. Almost all the repeat sections were elective. Thirteen patients had elective section for disproportion, and 13 elderly primigravidas had elective primary section without trial of labor.

When the maternity pavilion first opened, ether-chloroform mixture was used as the anesthetic for most vaginal deliveries and procaine spinal for most cesarean sections. Now cyclopropane, nitrous oxide, and oxygen are used for most vaginal deliveries, and this combination, plus thiopental (Pentothal) and relaxing agents, is used in the majority of cesarean sections. Tubal ligation was carried out at

the time of cesarean section in 20% of the women. All except 4 of those sterilized were multiparous. There were 479 babies delivered, including 3 sets of twins. Seventy-three (15%) weighed under 2,500 Gm. (5½ lb.) and were considered premature. Among the elective sections there were 16 (3.3%) premature babies, and of this group 3 died. Of the 479 babies, 6 (1.4%) were stillborn, and 25 (5.2%) died in the neonatal period. This resulted in a gross fetal loss of 6.4%. Among the neonatal deaths in all cesarean sections in this series, prematurity was the biggest problem. In this connection it is suggested that perhaps the maternal risk would not be too much increased if more women were allowed to commence labor before elective section was performed.

Studies in Prolonged Pregnancy: Part IV—Clinical Assessment. C. H. G. Macafee and G. Bancroft-Livingston. J. Obst. & Gynaec. Brit. Emp. **65**:7-15 (Feb.) 1958 [London].

Of 1,852 pregnant women who were admitted for delivery to the Royal Maternity Hospital, Belfast, between 1956 and 1957, 386 (21%) had pregnancies prolonged beyond 287 days, and 143 (7.7%) had pregnancies which exceeded 294 days. Among the 1,852 deliveries there were 81 stillbirths, an incidence of 4.4%. Among the deliveries of women whose pregnancies exceeded 287 days, there were 10 stillbirths, and among those of the 143 women whose pregnancies exceeded 294 days, there occurred 6 stillbirths (4.2%). There was one congenital abnormality (gross cardiac defect) incompatible with life, giving a corrected figure of 3.5%. Five neonatal deaths occurred after pregnancies lasting more than 294 days; in 4 of these 5 cases the fetus was abnormal, and in the 5th birth trauma seemed likely because of the difficulty encountered in the delivery of the infant weighing 4762.7 Gm. (10½ lb.). This incidence of stillbirths and neonatal deaths compared favorably with that previously reported, despite the fact that routine induction of labor did not figure in the treatment. Routine induction of labor 5 to 7 days after the calculated date is to be considered as meddlesome midwifery. Forceps delivery was indicated in 32% of the women whose pregnancies exceeded 294 days, as compared with the over-all hospital forceps rate of 15.6%. The cesarean section rate of 6% among the women with prolonged pregnancy was not higher than the over-all figure for the hospital. Thirty-three (23%) of the women in this group had a labor which lasted more than 24 hours, and in 18 of these meconium was present for varying periods of time. As the average duration of labor for primigravid women in the hospital is 16.9 hours, prolongation up to or beyond 24 hours is significant.

These data would suggest that mechanical difficulty plays an important part in prolonged pregnancy; the role of hypoxia in prolonged pregnancy, however, has been overemphasized. The significance of the presence of meconium at artificial rupture of membranes or during labor has been erroneously interpreted as resulting from fetal hypoxia due to placental insufficiency. Meconium as the result of hypoxia may be due to compression of the cord either as the result of prolapse or extreme shortening, not primarily to placental insufficiency. The presence of meconium during labor may indicate an earlier episode of fetal hypoxia, but if the fetal heart is undisturbed, one may adopt a conservative line of treatment. When meconium appears in a prolonged labor, cephalopelvic disproportion which may interfere with placental function must be excluded, as cesarean section may be the correct method of treatment. In the absence of disproportion it is only the occasional case which will give rise to anxiety, but careful observation of the fetal heart is essential, and, if necessary, a forceps delivery to shorten the second stage. The above advice is applicable regardless of the maturity.

PEDIATRICS

Some Common Medical Problems Encountered in Mentally Retarded Children. C. Drayer and I. Mauss. New York J. Med. **58**:670-674 (March 1) 1958 [New York].

Fifty retarded children, between the ages of less than 1 year and 16 years, were selected at random and studied regarding causation of mental retardation, nutritional status, susceptibility or unusual reactions to illness, congenital abnormalities, abnormal neurological findings, and accident proneness. Of the 50 children, 39 were not of the type with mongolism and 11 were of the type with mongolism. Seven (14%) of the 50 children had a birth weight of less than 2494.75 Gm. (5½ lb.), as compared with the normal incidence of 5 to 10%. Nine of the 11 mothers of children with mongolism were over 30 years of age at the time of delivery, confirming the frequent observation that mothers of children with mongolism are older at time of delivery than mothers of normal children. Developmental or embryologic causative factors of retardation were found in 10 children; birth trauma was considered a causative factor in 7, postnatal encephalitis in 4, a skull fracture sustained at the age of 1 year in 1, and a hereditary factor (lipochondrodystrophy) in 1. Causative factors were not determined in the remaining children.

There did not seem to be any significant deviation from the normal nutritional status. The number of children (25) with head circumferences well below normal was far out of proportion to what one would find in the general population. Only 3

children showed an unusual tendency to the occurrence of high fever, in contrast to the common belief that retarded children are prone to high fever. Twelve children either had a convulsive disorder or gave a history of convulsions. The convulsive episodes were followed by retardation in 2 of these. None of the children with mongolism had convulsions. Among the congenital abnormalities, strabismus was found in 16, congenital heart disease in 3, and extreme arching of the palate in 18. Twelve children (25%) showed no evidence of any congenital abnormalities. The incidence of congenital abnormalities in the 50 retarded children, however, seems higher than one would expect to find in the general population. Only 2 children showed a tendency to fall, but even these 2 did not sustain severe injuries in their falls. Twenty-seven children showed one or more abnormal neurological findings, such as abnormal gait, poor coordination, spasticity, athetosis, abnormal reflexes, and intention tremor. The authors are convinced that with proper management, appropriate group experiences, education up to capacity, and the aid of sheltered workshops more satisfactory adjustments can be made by many of the more severely retarded children.

Malignant Abdominal Tumors: Present Condition of Three Little Girls Three Years After Operation. L. Gubern Salisachs. Rev. españ. pediat. 14:39-46 (Jan.-Feb.) 1958 (In Spanish) [Saragossa].

Abdominal cancer in children is more frequent than is believed. It is curable, provided that the patient is observed within the period of operability of the tumor. The 2 most frequent types of malignant abdominal tumors in children are Wilms's tumor and sympathoblastoma. The subjects of this report are 3 girls, aged 4 years, 3 years, and 1 year respectively. The first patient had lost weight for 2 months before observation. An abdominal tumor was found by palpation. It grew rapidly to the size of the head of a fetus. Roentgenologically it appeared to be a renal tumor. Preoperative roentgenotherapy consisted of 10 sessions of 200 r each. This treatment was followed by 4 days of rest, after which a nephrectomy was performed. Biopsy showed a Wilms tumor. Postoperative roentgenotherapy consisted of 10 sessions of 200 r each. The second patient had an abdominal tumor which had grown rapidly for 4 months before observation. Clinical and roentgenologic examination showed a left-sided renal tumor. Nephrectomy on the left kidney was performed. Biopsy showed a Wilms tumor. Postoperative roentgenotherapy was given up to a total dose of 4,000 r. The third patient had abdominal colic and vomiting for 2 days before the observation. An abdominal tumor in the umbilical region was found by palpation. It seemed to be attached to the neighboring structures. A paravertebral tumor attached to the pancreas, the vena cava, the portal veins, and the choledochus was found and removed. A cholecystogastrostomy was performed 2 weeks after the operation to relieve obstructive jaundice. Biopsy showed the tumor to be a sympathoblastoma. Postoperative roentgenotherapy was started on the second day after the first operation. It was continued to reach a total dose of 2,500 r.

The 3 patients are apparently clinically cured at periods of more than 3 years and nearly 4 years. The biological time of cure of cancer in children without any recurrences for more than a year corresponds to that in adults of more than 5 years after the operation. The author emphasizes the need of not palpating the abdomen of children with symptoms suggestive of abdominal cancer. Abdominal tumors should be considered in the group of acute diseases of the abdomen. The abdomen should not be touched. In American hospitals as soon as children with acute abdominal disease suggesting an abdominal cancer are admitted, the patients are tagged with a note saying: "Please don't feel my tummy." By this means, dissemination of cancer cells is prevented.

Primary Hypophosphatemic Familial Vitamin-Resistant Rickets. M. Lamy, P. Royer, J. Frezal and H. Lestradet. Arch. franç. pédiat. 15:1-24 (No. 1) 1958 (In French) [Paris].

Observation of 3 patients with hypophosphatemic vitamin-resistant rickets prompted this study of the disease, which is hereditary and apparently familial in two-thirds of the reported cases. Two of the authors' cases appeared as phosphatic diabetes, which was transmitted as a dominant characteristic affecting various members of the two families in several generations; the third, which appeared as a renal aminophosphatic diabetes, was isolated and could not be proved to be familial. Severe clinical anomalies appear in one-third of the children of affected persons; consequently, since the disease usually begins in the 2nd year of life, the children of affected parents should be kept under observation from the age of 1 year on, so that treatment can be given, if needed, before dwarfism and severe skeletal deformities have time to become established.

The principal clinical signs of this form of rickets are functional disturbances, dwarfism, and skeletal deformities. Fatigability is often pronounced; osseous pains are not uncommon; and walking is delayed for several months. The muscular tone, on the other hand, is good, in contradistinction to the hypotony of ordinary avitaminic rickets. Another difference is the lack of hypocalcemic tetanic complications in primary hypophosphatemic vitamin-resistant rickets. The dwarfism, which becomes more and more apparent as the child grows, is

characterized by micromelia, especially of the legs. The osseous deformities are seen chiefly in the legs and in the spine, but they may appear elsewhere, e. g., in an olympic brow and in enlargement of the bridge of the nose. The roentgenologic signs closely resemble those of ordinary avitaminic rickets.

The biochemical signs are to be sought in the urine, the blood, and the feces. Calciuria is minimal, and the Sulkowitch reaction is either negative or weakly positive; phosphaturia is abundant, but albuminuria, melituria, and hyperaminoaciduria are lacking, and this distinguishes the condition from ordinary rickets and from the de Toni-Debré-Fanconi syndrome. Finally, the urinary sediment is normal. Analysis of the blood serum shows that the calcium level is normal or occasionally slightly lowered; phosphatemia is always low, between 10 and 30 mg. per liter; and the alkaline phosphatase is moderately elevated, usually standing between 15 and 25 Bodansky units. This level declines fairly rapidly, becoming normal again between the ages of 10 and 18. A defect in calcium absorption is revealed by examination of the stools. Renal function is generally normal, but the renal clearance of phosphates is high, as might be expected from the coexistence of hyperphosphaturia and hypophosphatemia, and the coefficient of tubular reabsorption of filtered phosphate is lowered, as demonstrated in one of the authors' patients, in whom it was 82% instead of the normal 92 to 95%. The response obtained to the intravenous perfusion of calcium gluconate (Howard test) in one of the patients led the authors to believe that the renal phosphatic diabetes in this patient was secondary and that the primary defect is prerenal. The disease pursues a chronic course. It continues to be active until the patient reaches the age of 15 to 20 years, when it enters a period of latency during which, although the patient remains dwarfed and presents multiple skeletal deformities, the subjective symptoms disappear, the roentgenologic anomalies are lessened, and the biochemical disorders are repaired, except for the hypophosphatemia. Relapses may occur during pregnancy or lactation.

Several theories have been advanced to account for hypophosphatemic familial vitamin-resistant rickets. It would apparently be premature to choose between them at the present time, but certain partial conclusions seem to be warranted. The primary factor is probably a defect in the intestinal absorption of calcium linked, not to a general insensitivity to vitamin D, but to the mechanism of calcium absorption, which does not depend on this vitamin. The second factor is hyperparathyroidism as in ordinary rickets; this is responsible for the increase in the renal clearance of phosphate and perhaps for the different anatomic aspects of the osseous lesions. Presumably, then, vitamin D in large doses acts by bringing about a discreet increase in the digestive absorption of calcium, perhaps by mobilizing calcium from the bones and, finally, by direct blocking of the parathyroids.

Treatment consists of vitamin D administration and osteotomy. Vitamin D (D_2 or D_3) should be administered uninterruptedly in large doses, adjusted to produce the highest phosphatemia possible without exceeding 111 mg. per liter of calcemia, or 400 mg. per 24 hours of calciuria. The object should be to find the dose that is effective without being toxic, and the child's parents should be instructed in regard to the signs of vitamin D intoxication, which is always to be feared. The primary purpose of osteotomy is to correct deformities of the lower limbs. The immobilization osteoporosis to which it leads has a definitely beneficial effect on growth in stature, on the diaphysial and epiphysial roentgenologic signs, and on the biochemical signs, producing, among other things, an abrupt drop in the alkaline phosphatase level. To prevent vitamin D intoxication, administration of the vitamin should be discontinued before and for some time after osteotomy. Continuance of the treatment during the adult period depends on the patient's tolerance for the disease; in most cases, however, it should be discontinued at this time.

Evaluation of Success of the Dietary Treatment with Casein Hydrolysate Poor in Phenylalanine for Oligophrenia Phenylpyruvica. R. Grüttner, F. Müller and H. Wallis. Monatsschr. Kinderh. **106**:41-45 (Feb.) 1958 (In German) [Berlin].

The authors report on 2 boys, aged 2 years and 3 months and 3 years and 3 months, respectively, and 1 girl, aged 1 year and 3 months, with oligophrenia phenylpyruvica, in whom determinations of the phenylpyruvic acid excreted in the urine were carried out and who were placed on a diet in which a casein hydrolysate to which tyrosine and tryptophan had been added was used as a protein source. The children received daily 2 to 2.5 Gm. of this hydrolysate per kilogram of body weight. Fat was given in the form of coconut margarine and olive oil (daily amount of 3 Gm. per kilogram of body weight), and carbohydrates in the form of grape sugar and wheat starch (daily amount of 10 Gm. per kilogram of body weight). Vitamin compound preparations and fruit juices also were given.

After 6 weeks' treatment with this diet, the excretion of phenylpyruvic acid in the urine was reduced from 187 mg. per 100 cc. to about 20 mg. per 100 cc. in the 2 younger children, i. e., the excretion of the phenylpyruvic acid was restored to normal. Control of the disturbance of metabolism thus was obtained in these 2 patients. In the 3-year-old boy, the excretion of the phenylpyruvic acid in the urine was considerably reduced but was not restored to normal; the "lightening and nodding" cramps, however, subsided. Much emphasis has been put on the

development of static and mental functions as an aid in the evaluation of the dietary therapy. A certain improvement in these functions was obtained in all 3 children, but the backwardness of the children remained so pronounced that severe idiocy was considered to be the right term for their condition. In the girl, a protein deficiency syndrome occurred after 3 months of the dietary treatment, manifested by edema and reduction of the serum protein level to 3.2 Gm. per 100 cc.; apparently mobilization of the autogenous protein resulted, which caused an increase in the pathological decomposition products of phenylamino-propionic acid (phenylalanine) and, therefore, an increased excretion of phenylpyruvic acid. The risk of such a complication has been stressed.

The authors agree with Armstrong and other workers that success of treatment with a diet poor in phenylamino-propionic acid may be expected only in children who are placed on this diet during the first months of life and in whom this treatment is continued throughout life. Irreparable damage of the substance of the brain must be taken into account when this therapy is instituted in the second or the third year of life; normalization of the mental functions than has become impossible.

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The Gastro-Oesophageal Region in Infants: Observations on the Anatomy, with Special Reference to the Closing Mechanism and Partial Thoracic Stomach. G. S. M. Botha. Arch. Dis. Childhood 33:78-94 (Feb.) 1958 [London].

The nature of the closing mechanism between the esophagus and the stomach has been studied chiefly in adults; the anatomy in the infant, which does not necessarily correspond, has not received the same attention. The diaphragm, lower esophagus, upper stomach, aorta, and surrounding tissue were removed en bloc from 115 infants. Every specimen was dissected, and drawings were made of the essential features. In age, the subjects varied from a 32-week-old fetus to an 8-year-old child. In the great majority the ages ranged from a few hours to 1 month. One fetus weighing 520 Gm. (1 lb. 2 oz.) and 1 girl of 13 years were also studied. The sexes were about equally represented. In addition to the dissected specimens, numerous studies were carried out in the autopsy room where the organs were examined in situ. Unlike in the adult, the hiatus in the infant was found to be of uniform size. It was small, so small that the narrowest portion of the esophagus could just pass through. The esophagus was gripped firmly. The outstanding features of the gastroesophageal region in infants and children were a small powerful hiatus with marked overlap and an oblique lengthy tunnel, a formidable phrenoesophageal membrane, and secure fixation of a narrow terminal esophagus. These features were considered to be mainly responsible for the superior gastroesophageal competence in infancy.

Since competence of the cardia and fixation of the esophagus are proportionately much better in the infant than in the adult, a partial thoracic stomach which causes vomiting immediately after birth is not merely a "slight herniation" but a major derangement. The author cites evidence to the effect that a partial thoracic stomach in infancy is a congenital abnormality in the great majority of cases. Differences in age, sex and familial incidence, clinical course, roentgenologic features, associated abnormalities, and outcome of surgery support the view that the mechanism of partial thoracic stomach in infancy and hiatus hernia in adults are not identical conditions. The noncommittal term "partial thoracic stomach" is preferred, as it is impossible in the great majority of cases to distinguish between sliding hiatus hernia and congenital short esophagus. The author concludes that evidence suggests that a large proportion of cases of partial thoracic stomach are due to congenital short esophagus, whereas, in contrast, hiatus hernia in the elderly is a degenerative manifestation in the evolution of the cardiac region.

Congenital Multiple Arthrogryposis. R. Joseph, D. Pellerin and J. C. Job. Semaine hôp. Paris. 34:525-536 (Feb. 24) 1958 (In French) [Paris].

Congenital multiple arthrogryposis is characterized by stiffness of the joints of the limbs, by paralysis with amyotrophies, and by muscular retractions. There may be associated malformations, some of which seem to depend on the muscular involvements. The condition is congenital and not progressive. On the contrary, the deformities present at birth sometimes become attenuated under the influence of mobilization. A brief review of the literature shows that before and after Stern, in 1923, introduced the now widely used, although not quite suitable, term "congenital multiple arthrogryposis," the condition was described under other terms. It is really a neuromuscular disease, and the authors feel that the following terms are the most suitable ones: "multiple congenital contractures," "congenital amyoplasia," and "deforming fetal myodystrophy." The causes of the condition are still unknown. The genetic origin often suggested does not fit all the facts. The hypothesis that it is an acquired embryopathy has not been fully confirmed. The authors believe that infants with the disorder recently observed by them illustrate the etiological problem.

One child was born after a normal pregnancy into a family without consanguinity or genetic anomalies. During the third month of gestation the mother had had daily contact with a child who was a carrier of poliomyelitis virus. However, at the time of delivery the virus was absent from mother and child, and the significant level of neutralizing antibodies did not show whether poliomyelitis had been transmitted to the mother during pregnancy. Two infants in a family of 4 children had typical

congenital multiple arthrogryposis. There was no consanguinity in the parents, and the family history revealed no anomalies comparable to multiple arthrogryposis. Biopsy of muscular tissue revealed fibers with degenerative lesions interspersed between normal fibers. A fourth child with arthrogryposis had 4 normal siblings, and again there was no consanguinity. In this child some of the muscles of the trunk also showed aplasia or paralysis.

The disorder is not extremely rare, over 250 cases having been reported. Pathological studies prove that the osteoarticular deformities are secondary to the atrophies. The latter are neurogenic. In 10 of 11 cases with complete anatomic studies, the muscular atrophy was accompanied by rarefaction or degeneration of the motor neurons of the spinal cord. The possible relationship of congenital multiple arthrogryposis to other congenital neuromuscular disorders is discussed. A disturbance acting on the motor neurons of the fetus before the 4th month of gestation is accepted as the pathogenetic mechanism of this disorder.

DERMATOLOGY

Morbidity Incidence of Certain Types of Dermatosis in 1946 and in 1956 at Istituto Dermopatico dell' Immacolata at Rome. R. Cavalieri. Cronache Ist. Dermopat. Immac. **12**:205-208 (Nov.-Dec.) 1957 (In Italian) [Rome].

Statistical data about persons with various types of dermatosis who received treatment at the outpatient department of the Istituto Dermopatico dell' Imacolata in Rome in 1946 and 1956, were compiled and assessed. Patients with common skin disorders were not included in this series. The disorders in decreasing order of severity were as follows: psoriasis, alopecia, varicose ulcer, trichophytosis, urticaria, herpes zoster, herpes simplex, vitiligo, epithelioma, lichen, erythema multiforme, and others. In 1946, 11,467 diagnoses and in 1956, 23,987 diagnoses were made. Morbidity incidence increased in 1956, as compared with 1946, for alopecia, epithelioma, erythema multiforme, herpes, lichen, psoriasis, and vitiligo. This statistical assessment probably reflects the present conditions. Decrease in the same period was noted for acariasis, erythema, leishmaniasis, lupus vulgaris, urticaria, dandruff, trichophytosis, and varicose ulcer. Statistical evaluation is probably accurate for the types of dermatosis which are caused by parasites. This improvement can be ascribed to hygienic and prophylactic measures introduced during the last 10 years. Decrease in the incidence of lupus vulgaris is largely due to the advent of antibiotics and of vitamin D_2. Decrease in the incidence of leishmaniasis at this institute does not correspond with actual conditions for the whole country. Reports from other areas where leishmaniasis is endemic in Italy still show a high incidence of the disease.

The Prophylactic Treatment of Poison Ivy Dermatitis with 3-n-Pentadecyl Catechol Using the Wheal Method. H. Keil. New York J. Med. **58**:57-59 (Jan. 15) 1958 [New York].

This communication records the results of making wheals in the skin with small doses of synthetic 3-n-pentadecyl catechol in the prophylaxis of poison ivy dermatitis. So far as the author knows, this is the first attempt to use this method to influence directly the "shock organ" (probably the basal layer in the epidermis) in this type of allergic contact dermatitis. This procedure was carried out in 28 patients who received in all 38 full courses of prophylactic treatment, each course consisting of 6 consecutive wheals made at weekly intervals. The optimal dose for the production of wheals was 0.2 cc. of 0.001% solution of synthetic 3-n-pentadecyl catechol in sterilized peanut oil. By placing the solution very close to the "shock organ" of the skin, an attempt was made to cause 6 mild attacks of localized and controlled poison ivy dermatitis. The clinical results observed with this form of treatment were as follows: Twenty courses were followed by complete freedom from attacks of poison ivy dermatitis; 16 courses were followed by transient abortive attacks; and 2 courses were regarded as failures. The clinical evidence, aside from the 2 failures, supports the view that the wheal method of prophylaxis with synthetic 3-n-pentadecyl catechol produces clinical hyposensitization. It is also probable that this hyposensitization lasts generally, but not always, for about 3 to 4 months after the treatment.

OPHTHALMOLOGY

Does Electric Convulsive Therapy Cause Cataract? M. Koskenoja and C. C. Runeberg. Acta ophth. **36**:102-109 (No. 1) 1958 (In English) [Copenhagen].

Since the introduction of electric (convulsive) shock therapy it has been suggested by some investigators that the therapy may either produce an electric cataract or accelerate the development of senile cataract. At the outpatient department of the University Eye Clinic of Helsinki, the authors observed a patient who complained of marked impairment of visual acuity after electric shock therapy. He had a bilateral cataract of a type suggestive of an electric cataract. Therefore, the authors were prompted to investigate whether an electric cataract is a complication after electric shock therapy, although in the case of this patient it was later demonstrated that electric therapy was not the

cause of his cataracts. Studies were made on the eyes of 633 patients in a mental hospital. Nine persons with typical congenital cataract were excluded. Electric shock therapy had been given to 237 of the patients, whereas 396 patients had not received such treatment. The statistical analysis of the findings did not demonstrate that electric shock therapy produces electric cataract.

Investigation into the Control of Trachoma in Sekhukuniland. J. A. Pratt-Johnson and J. H. W. Wessels. South African M. J. **32**:212-215 (Feb. 22) 1958 [Cape Town].

These studies were made in a native reserve in the northeastern Transvaal, with a population of 160,000 belonging to the Bapedi Bantu tribes. It was found that 100% of the population living on the "flats" had trachoma, but the inhabitants of the plateau or the neighboring mountains were free from the disease. Investigations suggested that the incidence of trachoma in this population depends on 2 factors: the prevalence of swarms of flies, which directly convey the infection, and the acute shortage of water, which prevents minimal hygienic precautions. Both of these factors exist on the "flats." Where the mountain dwellers live, on the other hand, there is no lack of water and only a few flies are found. Two important points were recognized during the treatment of trachoma: 1. Sulfonamides given parenterally and antibiotic ointment used locally arrest active trachoma and rapidly clear all evidence of the commonly associated secondary infection. 2. The hospital records show that this treatment is futile, because many children are treated as many as 4 times during the summer for subacute mucopurulent conjunctivitis. The authors doubt that a strain resistant to this therapy has developed, and they are unable to ascertain whether reinfection by flies includes the trachoma virus, or whether it is confined to commonly associated organisms, such as the Koch-Weeks bacillus. It appears that most emphasis should be laid on the prevention of trachoma by an attack on the fly plague and the provision of an adequate water supply.

OTOLARYNGOLOGY

Premedication in Clinical Audiometry: An Investigation of the Effect of Mephenesin Carbamate (Tolseram) on Normal Hearing Thresholds as Determined by the Conditioned Psychogalvanic Skin Response and Conventional Pure-Tone Audiometry. R. B. Strauss. A. M. A. Arch. Otolaryng. **67**:354-363 (March) 1958 [Chicago].

Twenty-four men, between the ages of 21 and 28 years, with normal hearing, were tested in 4 ways by means of a Latin-square counterbalanced order. Each person's hearing thresholds at 500 cycles per second (cps), 1,000 cps, 2,000 cps, 4,000 cps, and 8,000 cps were estimated by conventional pure-tone audiometry after the administration of mephenesin carbamate or a lactose placebo, as well as by psychogalvanic skin-response audiometry after the administration of mephenesin carbamate or a suitable placebo. To indicate hearing acuity, the psychogalvanic skin-response audiometric method uses changes in skin resistance in response to a pure tone (conditioned stimulus) which occur after the skin resistance of the person, whose hearing acuity is tested, has been conditioned by a slight electric shock (unconditioned stimulus). A statistical analysis of variance of the quantitative data indicated that mephenesin carbamate in the dosage used had no statistically significant effect on hearing thresholds as determined by either psychogalvanic skin response or conventional pure-tone audiometry. Furthermore, no significant differences between hearing thresholds of the same persons were found, whether measured by conventional pure-tone finger-raising technique or by psychogalvanic skin-response audiometry.

The rationale for this study stems from the inadequateness and unreliability of conventional means of testing the hearing of infants, children, malingerers, and persons with psychogenic deafness. Normally active young children and hyperactive patients with neuromotor disorders cannot be tested satisfactorily by psychogalvanic skin-response audiometry either, because their activity interferes with the correct interpretation of the galvanic responses. Since mephenesin carbamate, an orally effective, centrally acting, skeletal muscle relaxant, may be used without interfering with or significantly affecting hearing thresholds, a way is paved for further inquiry as to the effectiveness of the drug in reducing the activity of normal children and the hyperactivity of patients with neuromotor disorders, so that this drug may be utilized as premedication to facilitate hearing testing.

THERAPEUTICS

Long-Term Treatment of Angina Pectoris with Dicumarol. Z. Gabrielsen and J. R. Myhre. Circulation **17**:348-353 (March) 1958 [New York].

An attempt was made to register by use of "report cards" the daily amount of anginal pain and the weekly consumption of glyceryl trinitrate (nitroglycerin) tablets in 9 men and 1 woman, between the ages of 42 and 61 years, with normal blood pressure and with arteriosclerotic heart disease and angina pectoris, during treatment by alternating courses of bishydroxycoumarin (Dicumarol) tablets and placebo tablets. Acute myocardial infarction had occurred previously in 4 of the 10 patients. All the patients had had their symptoms for at least 1 year, and 4 patients had had symptoms for more

than 3 years. One died shortly after the initiation of the study, and only 6 managed to keep count of their glyceryl trinitrate consumption. The total number of bishydroxycoumarin courses was 24, 12 of them lasting more than 6 months during a total period of 2 years of observation. Graphic records of the values for pain, as calculated from the daily report cards, and of the values for the consumption of glyceryl trinitrate tablets did not indicate that treatment with bishydroxycoumarin had a greater effect than treatment with placebos on the cardiac pain in the patients with angina pectoris of more than 1 year's duration.

Fibrinolytic Treatment of Thrombo-Embolic Diseases with Purified Bacterial Pyrogens. P. Meneghini. Acta haemat. **19**:65-81 (Feb.) 1958 (In English) [Basel, Switzerland].

In an attempt to study the value of activating fibrinolysis by means of highly purified bacterial lipopolysaccharides, 58 patients with thromboembolic disease were given a proprietary preparation of a highly purified lipopolysaccharide derived from Salmonella abortus equi (Pyrexal) or a proprietary preparation of acetylated lipopolysaccharide derived from Escherichia coli. Thirty-eight of the patients had thrombophlebitis, which was complicated by pulmonary embolism in 5, 9 had peripheral arteritis, and 11 had postphlebitic syndrome. The patients received an initial intravenous injection of 0.2 mcg. of Pyrexal; for this purpose, the 2-cc. ampul containing 1 mcg. of the drug was diluted with 8 cc. of isotonic sodium chloride solution, and then 2 cc. of this dilution was injected. More recently, ampuls of 5 cc. containing 0.5 mcg. became available, from which small initial doses of 0.2 mcg. were readily withdrawn. Treatment with the second lipopolysaccharide preparation was started with a dose of 50 mcg. given intravenously (dilution of the the 2-cc. ampul containing 200 mcg. with 8 cc. of isotonic sodium chloride solution, and injection of 2.5 cc. of this dilution). Depending on the reaction of the individual patient, the dose of Pyrexal was increased by 0.1 to 0.2 mcg. per injection, and the dose of the other preparation was increased by about 40 mcg.; the required febrile reaction was thus obtained almost without exception. The pyrogen injections were generally given at intervals of 2 days to let the patient recover sufficiently from the shock. The injections were given every other day when the patient was not significantly affected by the fever therapy.

Treatment with the tested preparations had the advantage over that with vaccines and that for a similar fibrinolytic activity in that the febrile period was shorter and lasted only about 6 to 8 hours and that the undesirable side-effects were less pronounced. The rise of temperature occurred within about 1 hour after the injection; temperatures of 38 C (100.4 F) to 39 C (102.2 F) were often associated with intense rigor lasting for 1 hour. When the patient was given effective antipyretic premedication, the temperature rose only to 37.5 C (100 F). The therapeutic results were as satisfactory as those obtained with vaccines, which were reported on previously. In the patients with arteritis, the bacterial polysaccharides acted chiefly on the thrombosis, by which the arteritis was complicated, and promoted the establishment of an effective collateral circulation. Pyrogen-induced fibrinolysis brought about a suprisingly quick recovery both in patients with phlebothrombosis and thrombophlebitis and in patients in whom embolic complications had already occurred. The febrile reaction can be mitigated with the aid of antipyretic medication (especially sodium salicylate), which does not interfere with the activation of fibrinolysis. Combined therapy with anticoagulants and fibrinolysis elicited by bacterial lipopolysaccharides is advisable, since blood clotting and fibrinolysis are controlled by 2 different enzyme systems. Anticoagulants are valuable chiefly because of their preventive effect on thrombosis and its spread. The response to artificial fever therapy is so rapid that one can hardly question the thrombolytic process involved in the activation of fibrinolysis which results from this measure.

First Experiences with the Use of Meprobamate in the Therapy of Cardiovascular Disorders. F. Fontanini and A. Rivi. Minerva med. **48**:4499-4503 (Dec. 26) 1957 (In Italian) [Turin, Italy].

Usefulness of meprobamate as a psychotherapeutic agent has led the authors to administer it to 52 patients who have had cardiovascular disorders associated with psychoneurotic anxiety and tension state. Patients were divided into 3 groups. The first group was composed of 12 patients with functional cardiac disorders, the second of 21 patients with organic heart disease, and the third of 19 patients who had various types of hypertension associated or not with heart disease. The daily dosage was 500 mg. given in 1 or 2 tablets. The first group received meprobamate alone, whereas the others received the drug as an adjunct to the basic therapy, but with the exclusion of any other sedative.

Meprobamate produced partial or complete remission of neurotic symptoms among the patients of the first group, without bringing improvement to the patients who complained of depression. The states of anxiety and tension had not developed independently but were mostly associated with the heart disease in the patients of the second group. The results in this group were inconsistent; meprobamate had favorable effect on some patients and no effect on others with the same or a similar clinical picture. All patients of the third group (arterial hypertension) derived benefit from meprobamate at varying degrees. There was a slight de-

crease of high blood pressure and gradual remission of some subjective symptoms, among which were headache, palpitation, paracusis, nervousness, and irritability. Complete remission of subjective and objective symptoms was observed in patients with a mild form of hypertension. The drug was well tolerated by all patients. A certain amount of somnolence and drowsiness were the only side-effects noted. These disturbances were bypassed by decreasing the dosage of the drug. Meprobamate exerted only a slight or no change on the pulse rate and on the electrocardiograms in this series of patients.

Immediate Therapy for the Acute Attack of Asthma: A Comparison of Epinephrine and Orally and Intravenously Administered Prednisolone. H. H. Pinkerton Jr. and T. E. Van Metre Jr. New England J. Med. **258**:363-366 (Feb. 20) 1958 [Boston].

Prednisone and prednisolone provide relief for the asthmatic patient and are free from the salt-retaining qualities that characterize many related compounds. However, relief has not been evident until 6 to 72 hours after onset of therapy, and therefore supplementary use of faster-acting agents, such as epinephrine, has proved helpful. It has been suggested that the intravenous administration of the corticosteroids might shorten the time required to produce relief, and when a form of prednisolone for intravenous use became available, studies to compare the rapidity of prednisolone administered intravenously, prednisolone orally, and epinephrine intramuscularly in providing relief from wheezing in bronchial asthma were undertaken. The studies were carried out in the allergy clinic of the Johns Hopkins Hospital in the months from March, 1956, to February, 1957.

Thirteen patients received intramuscular injections of epinephrine, 13 a single intravenous injection of 33.5 mg. of prednisolone, and 14 a single oral dose of 33.5 mg. of prednisolone. Epinephrine provided more rapid relief from asthma than did prednisolone given either orally or intravenously. There was no significant difference between the responses to prednisolone given orally or intravenously within 3 hours of administration, although the 17-hydroxycorticosteroids occurred almost immediately after the intravenous administration of prednisolone but 1 to 3 hours after an oral dose. This suggests that the initiation of clinical response depends on more than plasma levels. Intravenous injection of prednisolone is useful when the oral route is contraindicated. There was no indication that epinephrine or prednisolone potentiated each other's effect on asthma. This is not surprising in view of the evidence that the effect of epinephrine is sympathomimetic and that of prednisolone anti-inflammatory. It is evident that epinephrine may be used to advantage to supplement prednisolone therapy. Therefore, the effectiveness of epinephrine should be maintained by instituting corticosteroid treatment before excessive use of epinephrine has induced drug resistance (tachyphylaxis).

PATHOLOGY

Demonstration of the Value and the Possibilities of the Official Method of Alcohol Estimation in the Blood by the Control Examinations Provided for by Legislation. H. Griffon and R. Le Breton. Ann. méd. lég. **37**:237-247 (Sept.-Oct.) 1957 (In French) [Paris].

The official method used in France for estimating the amount of alcohol in the blood, in which two standard procedures, Nicloux's distillation of blood and estimation of the nitrochromic alcohol by the Cordebard technique, are used, has been criticized on several occasions, not only by operators with little experience but also by expert biologists. The criticisms, however, are generally lacking in validity. Thus, it has been said that the official technique combines macroanalysis and microanalysis and that the quantity of distillate, about 40 ml., is needlessly large. It is true that only 2 ml. (not 1, as stated by the critic, since for accuracy the determinations must always be made in duplicate) is required for the chemical estimation of the alcohol in the distillate, but the other 38 ml. is useful because this amount makes it possible to prove, by the method of extraction of alcohol in a pure state, that the volatile reducing substances estimated by the chemical method are, in fact, composed of alcohol. Proof of this kind is often essential, not only when the analysis of the blood is delayed, as it may be during the vacation period, for example, but also when doubt exists as to its proper preservation and especially when it has been obtained from dead bodies. Mention of this contingency might well be made in the official stipulations.

The technique, now officially adopted, has been in use in the Toxicology Laboratory of the Prefecture of Police for 15 years and has proved to be perfectly adapted to the end in view. It produces results that are remarkably constant and so precise that the order of magnitude of the least favorable comparative error is barely more than plus or minus 5%, which for a biological technique is satisfactory. Determinations of blood alcohol which were made in 31 cases after a lapse of 10 months were perfectly consistent with the estimates initially made in the same cases—a fact which provides additional proof of the value of the method used in determining the blood alcohol and of the legislative measures surrounding such determinations. It would, however, be desirable to have supplementary documents providing for the separation of alcohol in the pure state, whenever the biologist deems it advisable,

and prescribing the procedure to be employed in sterilizing the skin and the equipment and prohibiting the use of volatile reducing substances for this purpose.

Bone Marrow Transplantation in Animals Exposed to Whole-Body Radiation. C. C. Congdon. J. Cell. & Comp. Physiol. **50**:103-108 (Dec. [Supp. 1]) 1957 [Philadelphia].

The author discusses experiments in which lethally irradiated animals were kept alive by intravenous injection of normal bone-marrow cell suspension. A quantity of blood-forming cells are removed from the bone marrow of a nonirradiated animal. The living cells are suspended in buffered isotonic solution of sodium chloride and injected intravenously into a lethally irradiated, isologous, genetically identical animal (donor and recipient belonging to the same inbred strain). It was established that blood-forming tissues are specific for irradiation injury. Adult isologous spleen that contains blood-forming cells, fetal liver, bone marrow, and sometimes whole embryos will cause recovery of the lethally irradiated animal, but adult liver, heart muscle, brain, endocrine glands, and other nonhematopoietic tissues will not promote recovery. The dose of hematopoietic cells necessary for recovery depends partly on the genetic relationship of donor and host. A problem of great current interest is whether the immune mechanism is transplanted along with the precursors of blood-forming cells. This is particularly important in trying to understand the delayed foreign bone-marrow reaction. When isologous bone marrow is given to the irradiated recipient, there is good 30-day survival at supralethal doses of radiation; and if the animals are observed for a year or so, there may be no additional mortality. However, bone marrow from a different strain or from a different species, such as transplantation of rat bone marrow to a mouse, may give good 30-day survival, but large numbers of the animals die subsequently.

Recovery from lethal irradiation injury in the bone-marrow experiment is caused by a rapid regeneration of blood-forming tissue that prevents infection, hemorrhage, and anemia. Evidence from chromosomal, histochemical, and immunological techniques demonstrates that the regenerated blood-forming cells and their products in the peripheral blood are descendants of the injected blood-forming elements. When the donor of the bone marrow is not genetically identical to the irradiated recipient, the transplanted bone marrow can be associated with a delayed immunological disorder that kills most of the irradiated mice many weeks after exposure.

Immunological Aspects of Homo- and Heterologous Bone Marrow Transplantation in Irradiated Animals. D. W. van Bekkum and O. Vos. J. Cell. & Comp. Physiol. **50**:139-156 (Dec. [Supp. 1]) 1957 [Philadelphia].

In this investigation the effects of homologous and heterologous bone-marrow grafts in mice and rats were studied after roentgen-ray irradiation with various doses. The results show that in mice homotransplantation and heterotransplantation are possible only after supralethal doses of radiation to the whole body. The failure of the transplantation after smaller doses of roentgen rays was thought to be caused by the survival of a few antibody-producing cells. The authors tested this hypothesis by injecting isologous lymphoid cells (from a genetically identical animal of the same inbred strain), together with rat bone-marrow cells, into irradiated mice. By means of various homologous and heterologous host-donor combinations, the authors conducted a quantitative study of the therapeutic effect of bone-marrow transplants in irradiated mice and rats. The results indicated that even after supralethal doses of irradiation the immunological defense system is not fully paralyzed. A delayed mortality occurs during the second and third months after irradiation in mice protected with homologous and heterologous bone marrow. The results of a quantitative study of the effectiveness of isologous, homologous, and heterologous bone marrow show that the number of cells required to protect the host from acute radiation death is related to the degree of antigenic difference between the donor and the host.

If functional grafts of homologous and heterologous bone marrow are to be tested, the recipients have to be submitted to supralethal irradiation of the total body. Even in these animals the defense against foreign tissues is not completely inhibited, but successful transplantation can be obtained when sufficiently large numbers of cells are injected, provided that the antigenic difference is not too great. The assumption that some reaction against the graft remains possible, even after relatively heavy total-body irradiation, is supported by the observation that small numbers of intact isologous lymph-node cells may prevent the successful transplantation of rat bone marrow in irradiated mice. Although irradiated rats could be protected satisfactorily with isologous bone marrow, no therapeutic effect has been obtained with mouse bone-marrow cells.

According to the data obtained on the presence of rat granulocytes and rat erythrocytes in the peripheral blood of mice protected with rat bone marrow, the foreign hematopoietic cells replace those of the host within a few weeks after the transplantation. In some cases, the host's hematopoietic tissues regenerate; this is accompanied by the reappearance of an immunological response against

the donor tissues. The delayed mortality is virtually absent after treatment with isologous cells. Transplantation of homologous and heterologous bone marrow causes a high rate of delayed mortality. Only a few delayed deaths were observed in F_1 mice treated with parent-strain marrow and also in C57BL mice treated with F_1 marrow. It is considered likely that the delayed mortality is related to immunological reactions. Theoretically, both antibody production by the host against the graft and, reversely, by the graft against the host's tissues appears possible.

RADIOLOGY

Solitary Pancreatic Lithiasis. H. Cosco Montaldo. An. Fac. med. Montevideo **42**:63-71 (May-Aug.) 1957 (In Spanish) [Montevideo, Uruguay].

Two cases of true solitary calculi of the duct of Wirsung are reported. The patients were women, aged 19 and 46 years respectively. In neither of the patients was a definite clinical diagnosis of pancreatic lithiasis made. The younger patient had symptoms of acute cholecystitis without jaundice. A cholecystography gave negative results. A cholecystectomy, a choledochotomy, and a retroduodenal-pancreatic décollement were performed. A calculus the size of a grain of corn, lodged at the pancreatic duct, was palpated and removed by duodenectomy and papillectomy. The gallbladder and the common bile duct did not contain any calculi. The patient was discharged in perfect condition. The older patient had symptoms of cholelithiasis with jaundice. A cholecystography gave negative results. A cholecystectomy, a choledochotomy, and a retroduodenal-pancreatic décollement were performed. The calculus palpated in the pancreatic duct was misjudged as if it were a pancreatic nodule of the head of the structure. It was left untouched. The gallbladder removed by operation contained 40 stones. A few days after the operation, while the cholecystogram was being reviewed, the image of a calculus, either pancreatic or at the common bile duct, was observed. Morphi-amylo-cholangiography was done 17 days after the first operation. It gave the clearest image of a calculus, which was lodged in the lumen of the pancreatic duct. The calculus was not removed, and it was asymptomatic. Morphi-amylo-cholangiography was again performed on the patient 2 years after the first operation. It showed that the calculus persisted unchanged in the same location and position as it was when observed the first time. The patient is in perfect condition.

The author directs attention to the importance of (1) retroduodenal-pancreatic décollement during biliary surgery which permits palpation of pancreatic calculi and (2) morphi-amylo-cholangiography for roentgenologic visualization of pancreatic calculi. Retroduodenal-pancreatic décollement in the course of biliary surgery is made by (1) opening of the peritoneum at the level of the external border of the upper half of the second portion of the duodenum, (2) décollement of this border in an extension of 5 or 6 cm., and (3) introduction of the index and middle fingers of the right hand for palpation of the pancreas and extrinsic palpation of the pancreatic ducts. The technique of morphi-amylo-cholangiography involves (1) giving the patient an injection of 1 cc. of morphine 10 to 30 minutes before administering the opaque substance, (2) taking 2 or 3 serial pictures at intervals of 3 to 5 minutes during the stage of spasm of the sphincter of Oddi induced by morphine, (3) giving the patient an ampul of amyl nitrite to inhale, and (4) taking 2 or more pictures during the stage of relaxation of the sphincter of Oddi produced by amyl nitrite. Cholangiography during the opposite stages of spasm and relaxation of the sphincter of Oddi permits a clear visualization of the whole biliary and pancreatic ductal systems. The author shows by an illustration the results of morphi-amylo-cholangiography in 1 patient whom he had observed personally. The illustration shows the complete filling of the biliary ductal system by the opaque substance and, by reflux, the filling also of the duct of the main and the accessory pancreatic ducts, giving a clear lacunar image of a solitary calculus lodged at the main duct. This is believed to be the first record of the sort in the cholangiographic literature of the world.

A Year's Experience with a Co ^{60} Radiation Therapy Unit. G. Cooper Jr. and J. M. Carter. Virginia M. Month. **85**:118-123 (March) 1958 [Richmond].

The authors discuss the physics of the radioactive cobalt (Co^{60}) unit and enumerate its several advantages over orthovoltage (250 kv.) roentgen-ray irradiation. They commenced to treat patients with the Co^{60} unit in July, 1956, and at the end of a year they had completed treatment of 231 patients with 236 tumors. Sixty-six of the tumors were in the head or neck, 41 in the thoracic cavity, 43 in the abdominal cavity, 60 in the pelvic cavity, 15 in the skeleton, and 11 in other locations. The comparison of Co^{60} radiation with orthovoltage irradiation must obviously be confined to immediate effects, since long-term results will not be available for several years. In the meantime it can be stated that the Co^{60} beam makes it possible to introduce into subsurface lesions significantly larger tumor doses, to introduce the same tumor dose in fewer days, and to accomplish these 2 important advances with little or no skin reaction and with much less bone-marrow depression and radiation sickness. The result is better palliation of incurable malignancies and perhaps a little higher cure rate. Radiation of the energy order

of the Co^{60} beam is to be preferred to orthovoltage irradiation in the treatment of tumors in the head and neck and in the thoracic, abdominal, and pelvic cavities whenever a large tumor dose is needed. The same is true of deep-seated tumors in the musculoskeletal system which need a large tumor dose. When it is necessary to introduce radiation through skin damaged by previous radiation, advantage can be taken of the skin-sparing effect of the high-energy, homogeneous beam, even though the tumor dose needed is not large and even though the lesion is immediately subcutaneous. The bone-sparing effect of the high-energy, homogeneous beam is particularly useful when children's skeletons with their highly susceptible growth zones have to be placed in a beam of ionizing energy.

Complications of Aortography: Factors Influencing Renal Function Following Aortography with 70 Per Cent Urokon. A. C. Beall Jr., E. S. Crawford, C. M. Couves and others. Surgery 43:364-380 (March) 1958 [St. Louis].

The increased number of reports in the literature on complications, predominantly renal, occurring after aortography, which has been commonly considered an innocuous procedure, prompted the authors to conduct studies on 51 female dogs and on 18 men and 1 woman, between the ages of 36 and 70 years, in an attempt to elucidate the factors related to the development of functional renal changes and renal damage after aortography. Determinations of glomerular filtration rate, renal blood flow, and water and electrolyte excretion were recorded. A 70% solution of sodium acetrizoate (Urokon) was used as contrast medium. Three variables with respect to its administration were investigated: (1) dosage used, (2) site of injection, and (3) alteration in hemodynamics in the region of the kidneys.

Observations made both in the animals and in man indicated that the immediate hemodynamic response of the kidney to sodium acetrizoate is vasoconstriction. This is manifested by depression of both the glomerular filtration rate and the renal blood flow. In the dog, this was only slightly more pronounced if the aorta was occluded below the renal arteries in the course of the injection of the contrast medium. In man, chronic occlusion below the renal arteries due to arteriosclerotic occlusive disease does not appear to predispose the patient to renal damage after the intra-aortic injection of sodium acetrizoate. Some persistence of the acute renal hemodynamic response was seen in both man and animal as long as 2 hours after aortography. Return to normal occurred in most instances after several days, unless the amount of contrast medium injected was large enough to produce anatomic and functional damage to the kidney. Accuracy in placement of the aortographic needle is of utmost importance. The injection should be made into the suprarenal portion of the abdominal aorta, since direct injection into the renal artery produces severe damage to the kidney. Apparently because of inherent vasoregulatory mechanisms in the renal circulation, renal blood flow is not increased after aortic occlusion distal to the renal arteries. Therefore, there is no increase in the contrast medium delivered to the kidney after injection of this material when aortic occlusion is present. However, when the sodium acetrizoate is injected directly into the renal artery, the entire dose reaches the kidney since there is no collateral circulation to bypass this organ.

It is considered highly significant that renal damage did not occur in 200 patients in whom aortography was performed by the authors with a dose of 25 cc. or less of 70% solution of sodium acetrizoate, unless the renal artery was directly injected. Renal damage occurred in 7 of the 100 patients who received more than 30 cc. of the contrast medium at an earlier time when proper dose was not appreciated. It would appear reasonable not to expect renal complications when doses of a 70% solution of sodium acetrizoate of 30 cc. or less are employed and direct injection of the renal artery is avoided.

PHYSIOLOGY

Effect of Weight Loss on Respiratory Functions. J. Salzano, R. V. Gunning, T. N. Mastopaulo and W. W. Tuttle. J. Am. Dietet. A. 34:258-264 (March) 1958 [Chicago].

Because of the paucity of information regarding the effect of weight reducing on physiological responses, this investigation was undertaken to determine the effect of weight loss on some respiratory functions. Studies were made on 12 women and 4 men, ranging in age from 22 to 37 years. Weight of the subjects ranged from 14 to 85% above average. Nutritionally adequate diets were used to produce a decrease in body weight calculated to proceed at the rate of 2 lb. per week. The following functions were studied before, during, and after the weight-reducing regimen: respiratory rate, tidal volume, minute volume, and oxygen consumption, at rest. In addition, the oxygen required to perform a given amount of work (1,250 kg.-m. per minute and 720 kg.-m. per minute for the men and women, respectively) was calculated. The resting respiratory rate was not significantly changed in the majority of the subjects by a reduction in body weight. The majority of the subjects showed no significant change in resting tidal volume. However, 6 subjects had a resting tidal volume which was significantly less than control, and 1 subject showed an increase.

Weight reduction was not followed by any significant change in resting respiratory minute volume in the majority of the subjects. Ten subjects had sig-

nificantly less resting oxygen consumption after weight loss, while 6 subjects showed no change. Ten subjects showed no change in resting oxygen requirements, calculated on the basis of milliliters per kilogram of body weight; 6 showed an increase. The oxygen required to perform a given amount of work was significantly decreased during the post-reduction phase of the experiment. A reduction in body weight was followed by a significant decrease in the oxygen required to perform a given amount of work when body weight was used as a metabolic reference standard in 10 subjects; in 6 subjects, there was no change. The oxygen debt caused by work performance expressed as milliliters was significantly reduced in 12 subjects; in 4 it was unchanged. Oxygen debt, expressed as milliliters per kilogram of body weight, was decreased in 9 subjects after weight loss; in 7 no consistent change was seen.

Size and Shape of the Gallbladder and Volume of the Liver in Immature and in Full-term Newborn Infants and in Infants in the First Year of Life. R. Bulgarelli and E. Bertolotti. Minerva pediat. 9:1512-1519 (Dec. 8) 1957 (In Italian) [Turin, Italy].

Capacity, shape, position, and malformation of gallbladder have been studied in 130 infants since 1955. Of these, 76 were immature newborn infants, 22 were full-term newborn infants, and 32 were infants in the first year of life. The authors define as immature those infants born before or during the 9th month of gestation and weighing not more than 2,500 Gm. (5½ lb.) at birth. During the first month of life the capacity value of the gallbladder in this series of infants was found to be 2.26 cc., the mean length value 3.8 cm., and the mean width value 1.4 cm. The gallbladder had a cylindrical shape in the immature and a pear-like shape in the full-term newborn infants. The lower limit of the gallbladder did not reach the lower surface of the liver in about three-fourths of the immature newborn infants; it did reach in slightly more than one-half of the full-term infants and infants in the first year of life. Among the 352 autopsies performed during the last 2 years, 2 instances of intrahepatic gallbladder were found. The gallbladder exceeded the physiological limits in 4 infants and was below these limits in 11. The left lobe of the liver decreased in volume and the right lobe increased in these infants during the first week of life. The ratio of the liver weight to the body weight gradually decreased in the immature newborn infants during the period between the 6th and the 9th month of gestation (from 4.44 to 3.45%). This ratio increased in the full-term newborn infants (4.1%) and gradually and slowly decreased afterwards until the third month of life was reached (3.97%).

PUBLIC HEALTH

The Caravan Problem. H. Mackenzie-Wintle. Med. Officer 99:119-120 (Feb. 28) 1958 [London].

The author made a survey of trailers (caravans) in the south Oxfordshire district. A questionnaire, as noncontroversial as possible, was sent to the owners of 498 trailers on sites and to 332 persons whose trailers were currently registered on individual licenses in the area. To this questionnaire only 38% replied in spite of an assurance that, since the forms asked neither the name nor the address of the replier, he or she could not be traced. Site-owners who were sent a copy cooperated in almost all cases. Almost half of the trailers were occupied by couples. The next largest group (23%) consisted of couples with 1 child, followed by people living alone (14%). These 3 groups comprised almost 85% of the total. Two trailers had 4 children each, 8 trailers had 3 children each, and 28 trailers had 2 children each. Reasons given for starting to live in a trailer were housing shortage (30%), financial reasons (16%), desire to be independent (14%), preferred living in trailer to living in rooms (11%), need of mobility because of job (9%), and other reasons (20%). In answer to the question: "If you could have a new house at a rent you could afford and not lose money on selling your trailer, would you take the house or stay in the trailer?" Sixty per cent would prefer a house, 33% would prefer a trailer permanently, and 7% gave indeterminate, illegible, or uninterpretable answers.

Summarizing his own views about trailers, the author states that they are not suitable for children; that they are always substandard housing accommodation, and the fact that people can acquire a taste for trailer living does not alter this fact; that trailer living probably causes most young couples to postpone having a family or limiting their family to an only child, both of which are undesirable; that in his own districts he gets about twice as many complaints of sickness being caused by living conditions in trailers as in houses; and that the law with regard to residential trailers is inadequate. The author admits, though, that for young couples, with both the husband and the wife working, trailer living is better than living with in-laws or in digs and that trailers often afford suitable accommodation for older persons. Housing authorities should on no account slacken their efforts to provide houses because of the number of people living in trailers; most of them are in trailers because they have to be, not because they want to be. The author suggests more comprehensive legal regulations on residential trailers than are now in force under the Public Health Act.

BOOK REVIEWS

A History of Nutrition: The Sequences of Ideas in Nutrition Investigations. By Elmer Verner McCollum. Under editorship of H. Bentley Glass. Cloth. $6. Pp. 451. Houghton Mifflin Company, 2 Park St., Boston, 1957.

Although to encompass the entire history of the science of nutrition in a book of 450 pages is an almost insurmountable task, the author, who has been responsible for much of the present knowledge of nutrition, has managed to do this admirably. The subtitle of the book gives one an insight into the type of material included. The author spent about 10 years reviewing the published literature of the last 200 years for the background material for this book and has confined his history to those thoughts and experiments which, in his opinion, opened new areas of discovery. The period covered is roughly the 200 years between 1740 and 1940. The author designates 1940 as the end of an era. Essentially, that was about the time in which the primary objectives delineated by the early workers in the field of nutrition were achieved, i. e., determination of what chemical substances constituted an adequate diet for man and domestic animals.

The author traces the development of new ideas concerning the constituents of foods and of the gradual realization of the relation of foods to health. In 1745, it was believed that man, except for the spiritual portion of his being, consisted of wheat gluten. As recently as 1900, it was the generally accepted belief that only carbohydrate, fat, protein, and certain inorganic salts were all that need be considered in determining the adequacy of the diet. In speaking of the great strides made in the science of nutrition, the author says, "The new knowledge brought about improvement of health and its attendant elevation of the status of human life above the sordid, to a degree scarcely equalled by any other agency concerned with the prevention or cure or disease. . . . Viewed from this standpoint, the rise of the science of nutrition is one of the greatest events in human history." A list of basic references follows each chapter. This book would be a valuable addition to the library of every physician, as well as to those of dietitians, nutritionists, teachers, and all concerned with the science of nutrition.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

Spezielle chirurgische Therapie. Von. Prof. Dr. Max Saegesser. Band II, Sammlung medizinischer Lehr- und Handbücher für Ärzte und Studierende. Fifth edition. Cloth. 128 marks. Pp. 1,476, with 2,384 illustrations. Verlag Hans Huber, Marktgasse 9, Bern 16, Switzerland; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1957.

This textbook of general surgery, written in German by a Swiss surgeon, is printed on paper of high quality, and the print is large and the binding excellent. The material is divided into 10 parts, including injuries and diseases of the head, injuries and surgical conditions of the neck, thoracic surgery, abdominal surgery, urology (male), surgery of the spinal cord and vertebrae, general surgical conditions of the extremities, surgical diseases of bones and joints, injuries to bones and joints, and, as a final part, delirium tremens and a general philosophical discussion on the management of the dying patient. This last chapter is most appropriate to a textbook of surgery, although no other treatise of surgery has included such material. All the subjects are dealt with in an up-to-date manner. There is no bibliography, but frequent allusions by name are made to well-known contributors to the current surgical literature of Europe and the United States. One of the outstanding features of the volume is the line drawings which profusely illustrate the text. For the practitioner who is familiar enough with German to be able to read this book without frequent recourse to a dictionary, it should afford a complete review of general surgery (neurosurgery and gynecology excluded). For the surgeon studying German, a perusal of this compendium would enable him to combine practice in reading this language with a review of the broad field of general surgery.

A Handbook on Diseases of Children Including Dietetics & the Common Fevers. By Bruce Williamson, M.D., F.R.C.P. Eighth edition. Cloth. $6. Pp. 483, with 117 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, Scotland; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

The eighth edition of this handbook of children's diseases has been revised and in part rewritten since its last edition was published four years ago. The sections on antibiotics and poliomyelitis have been brought up to date. The inclusion of appropriate treatment with steroids (except that such treatment is not mentioned for fulminating meningococcal in-

fections), the use of recently available orally given nonmercurial diuretics, and the mention of increasing caution with respect to the degree to which children are exposed to radiation are indications of most recent pediatric thought, but no mention can be found of the use of such valuable new drugs as reserpine and other tranquilizers. Some of the treatments recommended, such as the use of castor oil as a cathartic and radiation therapy for an enlarged thymus gland, are largely outmoded in this country. This book is essentially a miniature textbook, in that it attempts to cover the disorders of all the body systems of the child. This makes it possible to give only the highlights of the more common disorders and precludes even mention of many of the unusual conditions that the reader might seek in such a handbook. A section on disorders of the newborn infant is noticably lacking in information on the severe illnesses arising from disorders of the respiratory tract and central nervous system. More emphasis might have been given also to the special problems of the immature infant, since better care for this group offers the greatest hope of reducing infant mortality rates. The illustrations are numerous and excellent. The small size, easily readable print, and soft covers make it well suited for its purpose of a handy reference on pediatrics for the medical student, nurse, and general practitioner.

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Operative Surgery. Volume Six: Hand, Amputations, Plastic Surgery, Gynaecology and Obstetrics. Under general editorship of Charles Rob, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London, and Rodney Smith, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Cloth. $19.50. Various pagination, with illustrations. Butterworth & Company, Ltd., 88 Kingsway, London, W. C. 2, England; 1367 Danforth Ave., Toronto 6, Canada; [F. A. Davis Company, 1914-16 Cherry St., Philadelphia 3], 1958.

The editors have continued the policy of selecting outstanding British consultants and contributors in the preparation of this reference book. The format is attractive and conforms to that of the preceding volumes. Descriptive, accurate, and informative drawings are numerous and well placed. Each operative procedure is approached in a uniform manner by a description of the preoperative management, the operation, and the routine and special postoperative care. The authors have chosen their references chiefly from British publications. With such a large undertaking (an eight-volume compilation), references from the world literature would add character to the work. By cautious and thoughtful editing, the usual errors of multiple authorship have been avoided and a consistency of style has been maintained throughout. This publication fills a gap in the existing literature, and it is recommended for postgraduate students and residents and surgeons in nonteaching centers.

The Essence of Surgery. By C. Stuart Welch, M.S., M.D., Ph.D., Professor of Surgery, Albany Medical College of Union University, Albany, N. Y., and Samuel R. Powers, Jr., A.B., M.D., M.Sc.D., Professor of Experimental Surgery, Albany Medical College of Union University. Cloth. $7. Pp. 320, with 50 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1958.

A stimulating aspect of this excellent textbook is that operative surgery is discussed on the level of simplified basic factors with disregard for the present-day trend of superspecialization. The thesis that specific principles of surgery do not change regardless of the area under discussion is lucidly expounded. Although a surgical textbook can rarely be read from cover to cover, this book can be with interest and ease. It would be difficult to single out any one of the 12 chapters as being better than any other. The subject of body fluids and electrolytes is difficult to present, but the chapter dealing with loss of body fluids makes the subject understandable and interesting, and the following chapter, which discusses infection, comes to life with a freshness of style that is seldom seen in modern textbooks. The simple line drawings are custom made to the written material and depict the story with finesse. The authors are to be congratulated for writing a book than can be recommended unreservedly.

Shock and Circulatory Homeostasis. Transactions of fifth conference, November 30, December 1, and 2, 1955, Princeton, N. J. Edited by Harold D. Green, M.D., D.Sc., Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. Cloth. $4.75. Pp. 337, with 78 illustrations. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1957.

The 35 participants of this conference on shock and circulatory homeostasis included internists, surgeons, physiologists, pharmacologists, and biologists. The conference dealt primarily with the following subjects: experimental shock in relation to hepatic blood flow, bacteria, protection by chlortetracycline, germ-free rats, adrenergic, cholinergic, and ganglionic blocking agents, humoral factors, hepatic ferritin systems, hypothermia and chlorpromazine, and lymphatic adjustments. This book enables a large audience to share in the findings of this as in previous Macy conferences. The recording of the informal discussions gives the reader a sense of having been present at the conference. Particularly worthy examples of this are the discussions of criteria of tissue anoxia (p. 21) and of health (pp. 141-144). This should be read by all investigators interested in experimental shock and related phenomena. It is also recommended to those clinicians who enjoy periodic forays into the frontiers of biological and medical knowledge.

QUESTIONS AND ANSWERS

TUBERCULOSIS AND SUNLIGHT

To the Editor:—*A patient who has had active pulmonary tuberculosis, now arrested, is under the impression that she must avoid direct sunlight. Accordingly, she bundles up, regardless of how warm the weather, to avoid the sun. Is there any basis for such precautions?*

H. L. Herschensohn, M.D., Santa Monica, Calif.

Answer.—Sunlight has been employed in the treatment of tuberculosis since antiquity. During the early part of the present century, there were those who extolled its value as a therapeutic agent and those who opposed its use on the ground that it results in increased symptoms, including hemoptysis. LoGrasso and Balderrey conducted a carefully controlled and well-documented study (*Am. Rev. Tuberc.* 10:117, 1924). Prior to that time, personal opinion, too few and too short periods of observation, too much exposure, and other factors had resulted in the controversy. The LoGrasso and Balderrey study resulted in the following statement: "According to our experience, heliotherapy will not produce hemoptysis, increase the activity of the lesions, or reactivate it if judiciously employed." These workers reported that patients with pulmonary tuberculosis derived considerable benefit from heliotherapy when promptly administered. Despite these observations, the opinion still is sometimes expressed that sunlight is harmful, even to persons with arrested tuberculosis. However, there is no documented evidence that by avoidance of direct sunlight this patient is protecting herself against reactivation of the arrested disease. Long periods of exposure of the entire body to direct sunlight, resulting in sunburn, would not be good for her or anyone else. However, the amount of sunlight that reaches exposed surfaces in ordinary street clothing will cause her no harm.

PENICILLINS G AND O

To the Editor:—*What are the relative values of penicillin G and penicillin O?*

R. B. McBride, M.D., Dallas, Texas.

Answer.—Penicillin G is benzyl penicillin and is obtainable either as the sodium or potassium salt, as procaine penicillin G, or as benzathine penicillin G. The chief difference is in effectiveness and duration of action; procaine penicillin G persists in action about six times as long as penicillin G, whereas benzathine penicillin G lasts for about 30 times as long as penicillin G from equivalent intramuscular dosage. Potassium penicillin O is allylmercaptomethyl penicillin. There is not as much information available on penicillin O as on penicillin G. It does seem to have less allergic tendencies. Cautious trial of penicillin O is justified in patients sensitive to penicillin G in special conditions when penicillin treatment is necessary. The chief difficulty developing with penicillin G is an apparently increasing tendency to produce allergic reactions.

SJÖGREN'S SYNDROME

To the Editor:—*A woman, aged 30, has complained of burning, itching, and dryness of the eyes for about two and one-half years. In addition, she complains of dryness of the mouth and nose to a lesser degree. Even crying does not produce lacrimation. There is no disturbance of vision. The diagnosis has been Sjögren's syndrome. Treatment has consisted of methylcellulose, prednisone ophthalmic drops, pilocarpine given by mouth, various topical anesthetics, estrogen injections, prednisone and prednisolone, and orally given vitamin A. She has also avoided strong light and irritants, such as tobacco smoke and dust. To the time of writing, no benefit has been obtained with these measures. Please advise regarding additional therapy.*

M.D., Pennsylvania.

Answer.—Sjögren's syndrome consists of dryness of the eyes, nose, mouth, and throat, due to deficient secretion of the appropriate glands, with the frequent association of enlarged parotid glands and rheumatoid arthritis. The sex (90% female) and age (majority postmenopause) incidence suggests hormonal imbalance, and other factors frequently considered include nutritional deficiency, metabolic dysfunction, and rheumatic diathesis. However, the etiology remains obscure, and treatment is symptomatic. Histologically, the lacrimal glands show round cell infiltration and atrophy of secretory elements, with eventual fibrous scar tissue replacement. The severity of symptoms and the difficulty of treatment are proportional to the amount of functioning gland tissue remaining and the tear flow produced. Schirmer's test, with use of strips of Whatman's filter paper 5 mm. wide, gives the most convenient measure of lacrimal function. The nor-

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

mal tear production is considered to be 15 mm. or more of moistening in five minutes. As little as 5 or 6 mm. may be wet with few or no symptoms, but in severe cases there may be less than 1 mm. In refractory cases of markedly deficient tear production, extirpation of all four lacrimal canaliculi affords the best relief by promoting retention of what scanty tear flow is present and increasing the effectiveness of artificial tears. The technique is as follows: The area of the canaliculi is infiltrated with procaine hydrochloride injected with a fine needle. Both upper and lower puncta are dilated. The electrocautery needle is introduced 6 to 8 mm. into each canaliculus, and coagulation is produced. Occasionally, repetition of the procedure may be necessary. Care must be taken, especially in young patients, to ascertain that tear flow is actually impaired, or a permanent and annoying epiphora may result. Epiphora is rare if there is less than 5 mm. of tear production as measured by Schirmer's test.

CALCIFICATION OF INTERVERTEBRAL CARTILAGES

To the Editor:—*In a patient with a diagnosis of calcification of intervertebral cartilages, possibly due to some activity, what therapy would help retard this ailment?*

M.D., Wisconsin.

Answer.—Calcification of intervertebral cartilages is an incidental finding and is of no clinical significance, unless x-ray evidence shows that it actually protrudes. It represents only an end-stage in development. It is suggested that the inquirer look elsewhere for the cause of the condition for which he is treating this patient.

MYOCARDIAL INFARCTION AND RETIREMENT

To the Editor:—*A 63-year-old school bus driver was referred for an opinion as to recommendation for retirement. In July, 1957, he was stricken with typical symptoms of myocardial infarction, which was substantiated by an electrocardiogram. Since the original episode, he has been asymptomatic. He has lost 15 lb. but remains slightly obese. He has had no symptoms suggestive of cardiac disease. Physical findings are completely normal. The only evidence of the previous disease is in the electrocardiogram, which demonstrates a QS complex in leads V_3 and V_4. He does not wish to retire. Please comment as to whether this man should be permitted to continue driving a school bus.*

M. D. Reiter, M.D., Wheeling, W. Va.

Answer.—This question poses a social problem as well as a medical one. In answer to the medical portion of the question, the patient should be allowed to continue to work at a suitable occupation. From a medical standpoint, the effort involved in driving the school bus seems ideally suited to one who has recovered successfully from a myocardial infarction, but the wisdom of allowing such a patient to continue in such a job might be questioned for other reasons. This job places the safety and even the lives of other persons directly in his custody. Should a recurrent myocardial infarct result in disaster, criticism might justifiably be leveled at the person or persons who permitted this patient to continue in such an occupation.

Answer.—This question is not as simple as it seems. Such patients should return to their jobs, provided they do not endanger the lives of others. Certainly people who have recovered from episodes of coronary occlusion drive cars all the time, but once a man has sustained an acute coronary occlusion, he may develop another. Thus, the question is complicated by moral, legal, and compensation insurance aspects. For this reason the patient should not be permitted to return to any employment, such as driving a school bus, where the lives of others are in his hands.

PROTEIN-BOUND IODINE TEST

To the Editor:—*How can the protein-bound iodine test be declared an accurate measure of thyroid activity when there appear to be so many more or less imponderables connected with the patient's intake of iodine? These include the intake of iodized salt in quantities that are not too accurately measured and the frequent self-medication with vitamin-mineral combinations which contain iodine. Is the intake of iodine negligible in connection with this test? Should the patient be told to avoid these iodine-containing substances before having a protein-bound iodine determination done? If so, for how long?*

Paul E. Adolph, M.D., Wheaton, Ill.

Answer.—Ingestion of inorganic iodide may lead to a falsely and abnormally high protein-bound iodine value. Iodide ion combines loosely with serum albumin when circulating in high enough concentration and for sufficient time. This combination is precipitable with the protein precipitants used in the chemical procedure. In general, several milligrams of iodine must be ingested daily for a number of weeks before any significant increase in the protein-bound iodine level will result. No definite information is available about the time required to avoid this effect of iodide ingestion prior to a protein-bound iodine test, but probably three or four weeks is enough. However, in actual practice, high protein-bound iodine values are seldom seen from vitamin or iodized salt usage. The use of the butyl extractable iodine procedure, now clinically available, will circumvent the artefact created by iodide ion. The iodide is extracted from the carrier protein by this solvent but is removed

by an alkaline or other wash. Organic iodinated compounds are detected by both the protein-bound iodine and butyl extractable methods, and falsely high values are found when these compounds are present in the circulation.

UNSATURATED FATTY ACIDS FOR HYPERCHOLESTEREMIA

To the Editor:—*Please give information on the value of corn oil and sunflower oil in the treatment of hypercholesteremia. In what form and in what amounts should they be taken?*

M.D., New Jersey.

Answer.—Dr. Ahrens, of the Rockefeller Institute of New York, has found that the use of unsaturated fatty acids in the amount of 30% of the total caloric intake, under rigidly controlled dietary restrictions, will lower the blood cholesterol levels in those patients exhibiting hypercholesteremia. A reprint of the symposium on the subject of fats in nutrition, sponsored by the American Medical Association's Council on Foods and Nutrition and held in New Orleans in 1957, is available from the Council. Sunflower oil and corn oil are similar in their content of unsaturated fatty acids. About 90% of the oil consists of linoleic acid and oleic acid in a proportion of about 2 to 1. In giving such products to patients, it must be remembered that they are fats and, as fats, are a source of calories. Therefore, instead of adding them to the regular diet, it would probably be desirable to insert them into the diet in place of some of the fats now being used. It is emphasized that these products are still in the experimental stage and that there are bound to be wide variations among individuals in their responses to this type of therapy.

"KNOCK-OUT" DROPS

To the Editor:—*What is the composition of "knock-out" drops? Are they the result of someone's imagination and portrayed by theatrical people and novelists? What is the composition of any type of medicament which, added to a liquid (such as coffee or milk) or given separately, will produce rapid sleep hypnosis? In many instances, when treating patients it is necessary to give a rapidly acting hypnotic by oral administration when the hypodermic cannot be used. One patient, who is allergic to chloral hydrate and who is so emotionally unstable as to require a very rapidly acting "knock-out" type of medication, is afraid of hypodermic needles.*

M.D., Maryland.

Answer.—"Knock-out" drops are very real; chloral hydrate in solution can be added to an alcoholic beverage which covers the taste of the drug so sufficiently that the drinker, who probably has already had several drinks, is unaware of the drug. This consultant is not aware of any magic formula which, taken orally, will effect sleep rapidly without the patient being aware of its presence. As a general rule, those substances (with the possible exception of chloral hydrate), taken in therapeutic doses, which effect sleep quickly have an action of relatively short duration. Secobarbital sodium is bitter in solution. Whether the "allergy" of the patient is actually a dislike for the taste of the chloral hydrate, which can be given in capsule form, or a response to gastric discomfort, since the drug is irritating, is not stated. Actual allergy to the compound is rather rare. The irritation may be overcome by proper dilution.

PROPHYLAXIS OF AMEBIASIS

To the Editor:—*In the comment on prophylaxis of amebiasis, which appeared in the Queries and Minor Notes section of* The Journal *for Nov. 16, 1957, page 1518, the following advice was offered: "If diarrhea develops, bed rest, the frequent consumption of tea, rice, and applesauce, and the use of simple antidiarrhea measures, such as kaolin with pectin or bismuth preparations and possibly camphorated opium tincture (paregoric), will permit the disease to run its brief course. . . ." This advice should never be taken without reserve, for, though apparently innocuous, it may lead to very serious consequences. First of all, the term diarrhea denotes a symptom which may be part of a mild disease not yet classified, or, in the countries where amebiasis prevails, it may be among the first symptoms of a very serious condition, such as paratyphoid, bacillary dysentery, nonspecific gastrointestinal infections, or even food poisoning. How would one know what the diarrhea is going to develop into? The course of this disease may be brief; the lives of the patients may be equally as brief. Second, "refractory amebiasis," mentioned in the comment, if properly treated when the first symptoms appear, rarely becomes refractory. It is the policy of waiting which causes amebiasis to be refractory. In like manner, bacillary dysentery, if not treated properly at the onset, not infrequently continues into very troublesome chronicity. It might be difficult for physicians not in the tropics to identify cysts of Entamoeba histolytica, but when the disease is in the symptomatic stage, when mobile trophozoites usually abound, most physicians in the tropics can usually spot one in a matter of minutes. Why wait until the disease is chronic and difficult to diagnose and to treat? Is this a medical Monroe's doctrine?*

C. L. Chen, M.D.
Nakon Pathom
Thailand.